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Clinical and Translational Implications of an Emerging Developmental Substructure for Autism

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Abstract
A vast share of the population-attributable risk for autism relates to inherited polygenic risk. A growing number of studies in the past five years have indicated that inherited susceptibility may operate through a finite number of early developmental liabilities that, in various permutations and combinations, jointly predict familial recurrence of the convergent syndrome of social communication disability that defines the condition. Here, we synthesize this body of research to derive evidence for a novel developmental substructure for autism, which has profound implications for ongoing discovery efforts to elucidate its neurobiological causes, and to inform future clinical and biomarker studies, early interventions, and personalized approaches to therapy.
INTRODUCTION

The autism spectrum disorders (ASDs) are common conditions of childhood (Maenner et al. 2020) for which the vast proportion of population risk is attributable to inheritance (Sandin et al. 2017), mediated principally by polygenic risk. The sibling recurrence rate is one order of magnitude higher than the general population risk (Hansen et al. 2019), and the rate for the identical (monozygotic) cotwin of an individual with autism is 80 times higher than the general population risk (Tick et al. 2016). In the past five years, the association of numerous de novo mutations (germ line chromosomal rearrangements or DNA sequence variants) with autism has advanced our understanding of the biological underpinnings of ASD, but these mutations are individually rare and, by definition, do not account for the formidable inherited transmission of autism in the population. Moreover, most rare monogenic syndromes associated with autism are also accompanied by substantial cognitive impairment (Myers et al. 2020), which affects no more than one-third of all individuals affected by autism (Maenner et al. 2020).

Most children affected with autism are born to unaffected parents. Given the recurrence patterns observed in families, this is presumed to occur on the basis of genetic variants being carried by unaffected parents and transmitted to their offspring. This is possible when numerous allelic variants—each individually contributing only slightly to the total risk—accumulate to the level of a clinical threshold in a given offspring while being at lower than threshold (or otherwise compensated) in either or both of the parents. Polygenic mechanisms of causation are responsible for many complex inherited neuropsychiatric conditions and pose significant obstacles to the development of therapeutic interventions; it is currently impossible to simultaneously target a plethora of genes or their protein products—in ASD these number up to thousands and are believed to contribute to susceptibility in a given individual. So, in contrast to gene-based strategies for monogenic syndromes (e.g., an antisense oligonucleotide designed to disrupt overexpression of a specific gene),
an alternative approach for inherited polygenic syndromes is to identify intermediate phenotypes through which groups of genetic susceptibilities exert their influence to cause a condition.

A comparable example is the approach to biological therapy for attention-deficit/hyperactivity disorder (ADHD), a condition that commonly co-occurs with ASD and that is also highly heritable and largely a function of polygenic causation. For ADHD, pharmacologic and behavioral interventions targeted toward hyperactivity, impulsivity, and inattention have been successful in attenuating both symptomatology and the potentially severe public health consequences of the condition in adulthood (Lichtenstein et al. 2012). Another instructive example is hypertension, an elevation of the singular quantitative trait of blood pressure. The function of maintaining blood pressure can be decomposed into a finite set of underlying processes (e.g., vascular resistance, stroke volume of the heart, and fluid and electrolyte balance)—each with its own genetic and mechanistic structure—that participate in an intricate system of checks and balances. Targeting disruption in cardiovascular dynamics from this granular perspective has identified numerous levers for the therapeutic adjustment of blood pressure during disease states. In retrospect, it would seem statistically misguided at best to try to relate genes to blood pressure without resolving the relationships between specific gene sets and the disparate functions that are interacting with (and at times compensating) one another dynamically in a living system.

In this article we describe the manner in which diverse combinations of early-inherited liabilities may influence the development of autism across different affected individuals, and how such causal heterogeneity may contribute to the persistent difficulty in tracing autism to a common set of inherited genetic variants; the most recent attempts to relate polygenic risk scores to autism still account for less than 10% of the known heritability (Grove et al. 2019). Given the transmission of quantitative (subclinical) autistic traits in affected families (Constantino 2011, Piven & Palmer 1999), and the overlap of inherited liability between autism and other neuropsychiatric conditions at both the phenotypic (Jokiranta-Olkoniemi et al. 2019) and the molecular genetic (Grove et al. 2019) levels, we and others have considered whether specification of a developmental substructure might serve as a more appropriate model for understanding the effects of inherited influences on autism. Under such a model, autism (like hypertension) may arise from any number of distinct disruptions (or combinations thereof) to brain or developmental processes that contribute to human social development and behavior. Such a substructure might also explain why it has been so difficult to link common genetic variation to the singular phenotype of autism, especially if different subsets of patients represent different permutations or combinations of heritable atypicalities giving rise to phenocopies of a common syndrome. Clarification of the contributing components and their timing might allow for more precise approaches to early identification or treatment of individual cases, just as has occurred for the treatment of hypertension, when the physiologic underpinnings are more precisely understood.

As is the case for schizophrenia and Alzheimer disease, one window in which to explore the developmental substructure of a condition is the period of time before it develops; for autism this is from the time of conception through the first 12 to 18 months of life. In this article we review and synthesize new information about predictors of the condition that have been identified during this early period. Studies that address the developmental substructure of autism have yielded surprising new insights into early risk prediction and the mechanisms by which inherited susceptibility (engendered by polygenic risk) may contribute to specific brain and behavioral processes underlying normative social development. The component processes of such a substructure would be expected to interact with one another in complex, at times compensatory, ways (reminiscent of the checks and balances inherent in cardiovascular dynamics), a better understanding of which would promote discovery of reliable biomarkers and allow more precise tracing of the impact of specific profiles of polygenic liability on brain and behavioral development.
We note at the outset that, historically, attempts to parse the autistic syndrome into component parts have traditionally done so in a different way, i.e., by dissecting its characterizing symptoms, classically described as a triad of social deficits, communicative deficits, and repetitive behaviors (Wing 1981). At face value, these symptoms appear to be distinct and potentially independent from one another. Twenty years of research, however, have indicated somewhat the opposite: These symptom clusters, which by definition co-occur in autism, are tightly intercorrelated not only in individuals with autism but throughout the general population (Frazier et al. 2014), and they are extremely stable over the life course for all people (Wagner et al. 2019). Twin and family studies have demonstrated that the genetic causes of autism overlap with those of subclinical autistic traits (Robinson et al. 2011, 2016). Such traits aggregate among the unaffected family members of individuals with autism (Constantino 2011), and throughout the population the estimated heritability of subclinical autistic traits is nearly identical to that of autism itself (Constantino 2011, Robinson et al. 2011). This makes it unlikely that autism represents the coincidental overlap of symptoms with independent etiologies.

In contrast to strong intercorrelations between the characterizing symptoms of autism, some of its early behavioral predictors appear to arise independently from one another in the population (Hawks & Constantino 2020, Pohl et al. 2019). This is illustrated in Figure 1, which contrasts a

![Figure 1](image-url)

**Figure 1** Competing models for the causal substructure of autism. (a) In the traditional model, inherited liabilities corresponding to the three characterizing symptom manifestations of autism (the so-called autism triad) contribute to genetic susceptibility for autism. (b) In a reconceptualization informed by developmental research, permutations and combinations of independent inherited liabilities (A through X; none specific to a particular autism symptom domain nor, necessarily, to autism itself) contribute to an allostatic load for a singular latent quantitative trait (autism) that secondarily gives rise to the array of characterizing traits and features of the autistic syndrome. Notable implications of reconceptualization include a unitary factor structure for the manifest symptoms of autism (i.e., that they arise from a singular underlying biological deficit; see Frazier et al. 2014) and genotype-phenotype associations that will be more pronounced for the relationship between each inherited liability (A–X) and a substructural neurobehavioral trait (a–x) than for genotypic association with autism, especially if autism can arise from numerous combinatorial aggregations of a–x, the effects of which might be accentuated by de novo mutations, perinatal complications, or stochastic influences on brain development.
traditional conceptualization of genetic causation with what the new data suggest. Figure 1a depicts the former, in which inherited liabilities responsible for each symptom domain are theorized to co-occur within an individual to produce autism. Figure 1b depicts the latter, in which combinations and permutations of disparate, causally independent developmental liabilities engender a convergent latent liability (autism) that secondarily manifests in the three recognized domains of symptoms, usually in the second year of life, although the age at which these domains are recognizable and distinct as the syndrome we clinically recognize as autism varies from individual to individual. In this article we review the recent evidence for this reconceptualization and elaborate key implications for clinical care, early preemptive intervention, and future research.

COMBINATORIAL EFFECTS OF INHERITED LIABILITIES MAY UNDERLIE CAUSATION AND HETEROGENEITY IN FAMILIAL AUTISM SPECTRUM DISORDER

Complementing this picture of the genetic structure of autism, the genetic causes of the characterizing behavioral features of ASD overlap with those of subclinical traits of ADHD, developmental coordination disorder (DCD), and Tourette syndrome (Lichtenstein et al. 2010). At the level of clinical range symptomatology, autism is four times more common among the siblings of individuals with ADHD than in the general population (Jokiranta-Olkoniemi et al. 2019, Miller et al. 2019); in contrast, autism is only slightly more common among the siblings of individuals with intellectual disability than in the general population (Xie et al. 2019). A 2017 sibling study estimated that just over half of the recurrence of autism within a family can be accounted for by the presence of ADHD, DCD, or both (Mous et al. 2017); the same proportion of variance in autistic trait scores in the general population can be predicted by variation in subclinical traits of the same conditions in both school-aged children (Reiersen et al. 2008) and infants (Pohl et al. 2019). These observations are corroborated at the molecular genetic level—where substantial overlap between ASD and other common neuropsychiatric disorders has been identified (Brainstorm Consortium et al. 2018, Grove et al. 2019)—although the proportion of all causal variance accounted for in molecular genetic studies still remains much more limited than that captured in twin and family studies (i.e., genetic-epidemiological research designs). In general, the characterizing traits of these distinct neurodevelopmental syndromes (ADHD and DCD) are highly heritable and themselves continuously distributed in the general population. The observation that there may exist a set of inherited behavioral liabilities that contribute to multiple neuropsychiatric syndromes (e.g., ADHD and autism) is consistent with the phenomenon of pleiotropy (the production of two or more apparently unrelated effects of an underlying causal influence). Pleiotropy has been repeatedly observed among patients with highly deleterious single-gene mutations—where loss of function in the same gene may result in intellectual disability in an affected individual in one family, epilepsy in another, autism in another, and so on. In some cases the cause of such pleiotropic outcomes has been traced to the interactions between disease-causing mutations and background genetic characteristics of a family, which determine whether the mutation will result in clinical impairment in one or more disability domains (Finucane et al. 2016).

A corollary of the observation of pleiotropy—whether at the level of familial liability or specific molecular genetic susceptibility—is that any individual case of autism may arise from a distinct combination of contributing liabilities. For example, both polygenic risk and rare monogenic variants can contribute additively to autism susceptibility within an individual (McKenna et al. 2018, Weiner et al. 2017). The search for pleiotropic developmental contributors to autism risk represents a major departure from traditional approaches to elucidating its origins, which have historically focused on factors that are specific to autism, an investigative bias that has unfortunately
constrained the search space for causal pathways leading to the condition. In retrospect, the potential contributions of non-autism-specific liabilities to the development of autism should have been recognized long ago when it first became apparent that disparate monogenic syndromes (e.g., Fragile X syndrome, tuberous sclerosis) commonly, but not always, give rise to phenocopies of the autistic syndrome. To this end, the common disorders that exhibit genetic overlap with autism (DCD and ADHD) have been historically regarded as comorbidities, a potentially misleading characterization when considering that they may actually represent contributing causes of autism (Hawks & Constantino 2020). Thus, heritable neuropsychiatric traits of other conditions that have now been shown to predict autism (occurrence, familial recurrence, or both) represent a first set of candidates for an underlying developmental substructure for the syndrome.

**Figure 2** illustrates four frameworks within which inherited liabilities that contribute both to autism and to an example disorder (ADHD) can be conceptualized.

A second candidate contributor to a developmental substructure for ASD is atypicality in social visual engagement. This has been ascertained primarily by eye tracking infants’ viewing of dynamic social scenes in the first 18 months of life, beginning prior to the time when overt pathognomonic deficiencies in eye contact are first appreciable in most children with autism. Jones & Klin (2013) observed that, among infant siblings of children with autism, decline in visual orientation to eyes over serial measurements began in the second month of life and predicted autism recurrence as well as the severity of social symptomatology among affected children. The developmental interval at which the contrast between later-born siblings with and without autism peaked was approximately 18 months of age, when low eye- and mouth-looking were found to be near universal in two replication cohorts of 18-month-olds with autism (Constantino et al. 2017). Using identical methodology, measurement of social visual engagement among epidemiologically ascertained, 18-month-old infant twins from the general population revealed two significant qualifications of the association: (a) Approximately 10% of typically developing infants in the general population—children who did not go on to develop autism—displayed levels of visual social disengagement (low eye-looking) in the atypical range that characterized toddlers with autism, suggesting that low eye-looking may be necessary but not sufficient to engender autism. (b) The degree of eye-looking was continuously distributed in the general population and exquisitely heritable, both at the level of total proportion of visual attention allocated to eyes/mouth and at the level of moment-to-moment pathways of visual fixation in response to dynamic social scenes (Constantino et al. 2017). Taken together, these findings suggest that atypicality in social visual engagement represents a common inherited developmental liability to autism, possibly with higher positive predictive value among siblings of affected individuals (in whom other independent inherited susceptibilities to ASD may be present) than in the general population. Variations in patterns of social visual engagement constitute individual-specific differences in the manner in which children assimilate socially salient information from the visual environment. Johnson et al. (2015b) have reported several convergent findings supporting a general hypothesis that such individual differences may relate to critical adaptive developmental mechanisms (such as niche construction) that contribute to the emergence of autism. Rather than invoking a notion of determinism or inevitability, this view of autism as a developmental adaptation to genetic susceptibility and its consequences is aligned with observations of the genetic, developmental, and symptom structure of autism described above.

A third candidate contributor to the developmental substructure of autism is polygenic liability specific to ASD, intergenerationally transmitted and indexed by subclinical autistic traits (Constantino 2011, Lyall et al. 2014). In 2019, we observed that such traits in parents are independent of other developmental predictors of autism within individuals (i.e., variation in motor coordination and attention in their offspring) and that all of them additively predict variation in
Figure 2
Four possible models of the developmental emergence of behavioral symptoms of ASD and ADHD. For simplicity, bidirectional interactions between genetic and environmental risk factors, intermediate phenotypes, and behavior over developmental time are not shown. (a) ASD and ADHD are associated with condition-specific liabilities; in addition, there are some inherited liabilities that specifically lead to comorbid ASD and ADHD. (b) ASD and ADHD are caused by a combination of transdiagnostic inherited liabilities and condition-specific liabilities. (c) Common inherited liabilities and adaptive processes are activated at condition-specific points in development. Comorbidity is created by a longer period of activation. Condition-specific genetic and environmental factors affect the timing of expression of common inherited liabilities. (d) Inherited liabilities for ASD and ADHD are condition specific but require the absence of condition-general protective factors in order to be expressed. Here, comorbidity simply results from the true statistical overlap of the presence of inherited liabilities for ASD and ADHD. Figure reproduced with permission from Johnson et al. (2015a). Abbreviations: AD, adaptive response; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; GE, genetic and/or environmental risk factor; PF, protective factor; RM, risk marker.

quantitative autistic trait variation among the children (Pohl et al. 2019). Evidence for the manner in which ASD-specific risk interacts with the effects of other developmental predictors is still emerging, through studies that systematically explore the effects of joint liability, how pronounced and how early the liabilities must manifest to predict adverse clinical outcomes, and that compare prediction in the general population to within-family recurrence among multiplex autism families (Hawks & Constantino 2020).

All of the abovementioned candidate contributors to the developmental substructure of autism lie within the realm of behavioral variation. An exciting new generation of studies, more limited
in sample size because of the technologies involved, is beginning to identify neural signatures of the condition, for which time will tell whether the respective phenotypes add predictive power or overlap with the predictions made by early behavioral observations. Either way, these studies hold the promise of profound new insights into mechanisms by which genes and behavior are linked in the causation of ASD. Brain overgrowth (Hazlett et al. 2017, Lee et al. 2020) and atypical cerebrospinal fluid (CSF) accumulation (Shen et al. 2017, 2018) ascertained by serial brain magnetic resonance imaging have been identified as early biomarkers of risk for autism, findings that are being further explored in active prospective studies in the United States and the United Kingdom. In the realm of functional brain activity, whole-brain signatures of neural complexity and communication (Gabard-Durnam et al. 2019, Haartsen et al. 2019) and atypical electrophysiologic or hemodynamic responses to social experience (Jones et al. 2016, Lloyd-Fox et al. 2018) are important candidate predictors that are also under intensive study (see below).

A final robust predictor of autism across nearly all of its diverse genetic causes—a notable exception being rare, highly damaging single-gene mutations engendering autism, intellectual disability, and dysmorphism (Miles et al. 2005)—is male sex. Many clues to the nature of the universally observed 3:1 male-to-female (M:F) ratio in autism arise by the time the disorder first develops (second year of life; see Halladay et al. 2015), when sex hormone levels are essentially identical for males and females. Importantly, the M:F recurrence ratio within families is the same as the population-wide sex ratio for the condition, indicating that the sex differential expression of inherited risk operates within and across disparate pathways to familial autism described herein. This observation has given rise to theories about a female protective effect for autism. Somewhat inconsistent with this model, however, is the repeatedly demonstrated absence of a Carter effect for clinical autistic syndromes, meaning that the family recurrence rate in relation to an affected female is generally equivalent to that in relation to an affected male and that sisters of affected individuals do not exhibit a significant increase in risk for autism to offspring in comparison to brothers of affected individuals (Bai et al. 2020). These data favor a hypothesis of greater male sensitivity to the phenotypic effects of genetic susceptibility in relation to the mean risk population wide (rather than a female protective effect per se), or of greater variability in the effects of risk genes in males versus females, with affected individuals (male and female) exhibiting a likelihood of reproduction that is much lower than average. Specifying the mechanism of sex-differential expression is a high priority for ongoing research given the potential magnitude of impact of treatments if they were capable of targeting convergent mechanisms of either resilience or sensitivity parsimoniously driven by sex.

CLINICAL AND TRANSLATIONAL IMPLICATIONS

Understanding the origins of autism sets the stage for a developmental approach to autism science, from genetics to brain development to behavior (see also Thapar & Riglin 2020). To achieve this vision, researchers must work toward identifying a more complete list of contributing influences and understanding how inherited liabilities operate together to incur risk for autism, as well as mapping the interactions between inherited polygenic susceptibility, penetrant de novo variants, and environmental adversity in the accumulation of risk for clinical autistic syndromes.

Implications for Next-Generation Clinical Research Studies of the Development of Autism

Although we propose several candidate inherited liabilities above, there are likely many more to be identified. The developmental footprints of specific inherited liabilities will probably be
identified in the period of development prior to the emergence of diagnostic symptoms, before they become confounded by downstream effects of the experience of autism itself. Prospective longitudinal studies of infants with older siblings with ASD have convincingly shown that behavioral symptoms of ASD emerge gradually over the first three years of life (Jones et al. 2014, Tiede & Walton 2020). In the first six months, symptom-relevant behaviors are nearly absent in infants with later ASD; there is then a gradual decline in social interest and communication (possibly reflecting a near-universal profile of regression in these domains; Jones et al. 2014, Ozonoff & Iosif 2019) such that by 12 to 14 months of age behavioral measures of autistic traits are moderately predictive of a later diagnosis (Pierce et al. 2019). Early autism diagnoses are typically maintained for life (McCauley et al. 2020); the proportion of children with ASD who receive a diagnosis increases with time and stabilizes around age 3 (Ozonoff et al. 2015). However, even in prospective studies of ASD some affected children are not definitively diagnosed until mid-childhood (Ozonoff et al. 2018). Variability in the timing of diagnosis even within prospective studies reflects heterogeneity in the duration of apparent near-typical development before significant delays or regression becomes clear (Pearson et al. 2018). Taken together, this literature suggests that autism-related variation in social development reflects a developmental process that can be variable in timing but that unfolds and stabilizes over the first few years of life. Of note, few studies have directly examined the coupling between the emergence of social communication and the restrictive/repetitive behaviors over this period; cross-domain coupling methods such as parallel process models will be important to test whether the early coalescence of characterizing traits and features of autism emerges in a uniform way across individuals and how the emergence of symptoms relates to the neurocognitive systems that shape early development.

In addition, a variety of other candidates represent good targets for further investigation. For example, alterations in basic sensory processing, including speech perception, have been recognized as part of the core autism phenotype (Edwards et al. 2017, Robertson & Baron-Cohen 2017, Tryfon et al. 2018). Evidence indicates that sensory atypicalities emerge in the first year of life, with a general pattern of exaggerated reactivity to simple sensory stimuli in infants with later autism [e.g., larger constriction of the pupil in response to bright light (Nyström et al. 2018), more accurate identification of a distinct visual object among homogenous distractors (Cheung et al. 2018), and exaggerated neural responses to repeated sounds (Kolesnik et al. 2019)]. Such alterations could have cascading effects on later development by affecting the critical sensory systems through which infants learn about the world. Furthermore, converging evidence suggests reduced specialization of social brain regions, including decreased responsiveness to naturalistic social interactions in key temporal brain regions (Braukmann et al. 2018, Lloyd-Fox et al. 2018) that typically specialize for social processing within hours after birth (Farroni et al. 2013), in young infants with later autism. These disruptions to social brain specialization could be a downstream consequence of the reductions in social engagement discussed above (Klin et al. 2015); alternatively, they may arise from difficulties in sensory processing of specific perceptual features like structural details of the face (Jones et al. 2016) or syllables within language streams (Seery et al. 2013). Regardless, reduced specialization in key brain regions could compromise or reflect differences in the efficiency with which social interaction is understood. In the second year of life, another potential liability emerges under the guise of greater internally directed attentional focus. Possible manifestations of this include slower shifting of attention to a novel stimulus when interest is already captured (Elison et al. 2013, Elsabbagh et al. 2013) and increased connectivity in the alpha range (suggestive of greater internal focus) while viewing dynamic videos (Haartsen et al. 2019). Such focus could be related to the monotropism described in first-person accounts from autistic people and may reduce the influence of social partners in shaping children’s attentional focus.
The degree to which these candidates represent independent inherited liabilities or are actually manifestations of a common process is a critical next step for investigation. Work to combine different predictors and examine their joint or individual effects remains rare; however, emerging evidence from both statistical modeling (Bedford et al. 2012) and machine-learning (Tye et al. 2020) approaches indicates that social and nonsocial predictors may act additively to raise liability for later autism. Sophisticated developmental modeling will be required to move from this broad profile of individual susceptibilities toward a coherent map of autism risk that would allow for the possibility that disparate developmental competencies may include nuanced capabilities for compensation (i.e., checks and balances in brain and behavioral development that allow deficits in one domain to be buffered by adjustments in others). Finally, some predictors of later autism in infants may be neural precursors of the behaviorally expressed subclinical autistic traits that run in families (see above). One way to examine this is to test how putative liabilities vary with dimensional autistic traits measured among first-degree relatives. In one example, Jones et al. (2016) showed that several measures of social attention predicted later ASD within a longitudinal cohort of infants with ASD. The same markers were associated with parental variation in heritable autistic trait measures within a population of neurotypical infants (Jones et al. 2017b). As discussed above, work in general population samples may be particularly important because it allows researchers to disentangle markers of autistic trait liability from markers of pleiotropic developmental disruption.

Integration of molecular genetics remains one of the most powerful tools we have for interrogating a condition that is as strongly inherited as ASD. As in clinically referred samples, both polygenic risk and chromosomal rearrangements relate to autism status within cohorts with family histories of ASD (D’Abate et al. 2019); thus, examination of the relation between genetic variation and putative inherited liabilities with infant sibling samples is tractable (e.g., Gui et al. 2020b). However, it may be problematic to exclusively use existing polygenic risk scores (PGRSs) for this endeavor because they are calculated on the basis of categorical diagnosis. Generating PGRSs for quantitative measures of autistic traits may be a more powerful approach, particularly for identifying the neurocognitive basis of the familial aggregation of behaviorally expressed subclinical autistic traits (Constantino 2011, Warrier et al. 2019). Further, additional genes may be associated with individual inherited liabilities but were missed in PGRS generation studies because they are too weakly associated with categorical diagnosis; large-scale infant genetics consortia could also be used to identify new risk genes for particular neurodevelopmental liabilities. An alternative approach may be to use network analysis or to generate PGRSs for particular suites of genes on the basis of their functional expression profiles at key developmental stages or within key brain regions (e.g., Parikshak et al. 2013) and to examine their association with transdiagnostic phenotypes (Sullivan & Geschwind 2019). Finally, integrating epigenetics may be important (Gui et al. 2020a) because measuring gene expression may add critical mechanistic insight to the development of genotype–phenotype relations (Sullivan & Geschwind 2019) while recognizing that the ascertainment of gene expression in peripheral tissues is at best an indirect reflection of such variation in brain, which is experimentally inaccessible except in postmortem samples.

Cross-diagnostic examination of the early predictors of later neurodevelopmental traits is also critical (Hawks & Constantino 2020), because it is likely that both distinct and common inherited liabilities for different neurodevelopmental disorders are detectable from infancy, as depicted in Figure 2. Indeed, researchers have begun to prospectively follow cohorts of infants with family histories of autism, ADHD, or both (Begum Ali et al. 2020) and to examine multiple neurodevelopmental outcomes within each cohort (Shephard et al. 2019). Such research has identified some predictors that appear unique to co-occurring conditions such as ADHD and anxiety within cohorts of infants with a family history of ASD (e.g., Ersoy et al. 2020, Gui et al. 2020b, Miller
et al. 2019, Shephard et al. 2019). One domain that is consistently related to a broad range of developmental outcomes is effortful control/executive functioning (Moffitt et al. 2011). Effortful control refers to a set of higher-level regulatory skills that shape cognition and affect in the service of abstract goals and that emerge gradually during development (Hendry et al. 2016). In general, better effortful control skills appear protective against ASD, ADHD, and anxiety (but not callous-unemotional traits); this may act in interaction (rather than additively) with other putative inherited liabilities. Alternatively, deficits in cerebellar function provide highly parsimonious candidates for widely distributed impairments in the developmental capacity for error-based learning or predictive modeling (von der Lühe et al. 2016), social motivation (Clements et al. 2018), and specific aspects of cerebellar learning that might exert joint abnormality in the domains of social and motor functioning (Nyström et al. 2018, Valnegri et al. 2017). Notably, Limperopoulos (2010) has described a previously underrecognized form of cerebellar parenchymal injury in up to 20% of extremely preterm infants, a group that has an elevated risk for developing ASD. Moreover, infants with rare, isolated cerebellar hemorrhages have highly elevated rates of ASD outcome, which suggests that cerebellar dysfunction represents a convergent neural abnormality that may tie together disparate manifestations of social and motor disabilities—including oculomotor function mediated by cranial nerve nuclei under cerebellar control—in the early development of autism.

Advancing New Understanding of a Latent Trait Encompassing Autism-Related Variation in Human Social Development

The proposal of a unitary dimension underlying the spectrum of autistic traits does not necessarily imply returning to a traditional single-deficit model of autism. Single-deficit theories traditionally proposed one cognitive or brain system that played a substantive role in autism (while often acknowledging that other systems may play a smaller role) and have been broadly criticized for both their empirical failures and their focus on a simplistic medical model of autism (Astle & Fletcher-Watson 2020). Most larger studies of autism show modest or absent case/control differences on measures associated with leading single-deficit accounts (e.g., Frazier et al. 2017, Moessnang et al. 2020, Muth et al. 2014), with effect sizes decreasing by as much as 80% over time (Rodgaard et al. 2019). The substantial heterogeneity in the degree, direction, and nature of brain and cognitive differences shown by each individual with autism has popularized approaches that involve summing individual deviations across multiple neurocognitive measures (already used routinely at the clinical level) (e.g., Jacob et al. 2019, Marquand et al. 2019, Zabihi et al. 2019) and disaggregating groups with autism into different stratified subtypes (Wolfers et al. 2019). Our conceptualization of autism-related variation in social behavior as a latent trait does not necessarily imply that this trait can be localized in one area of the brain in all individuals or that it encompasses a single domain of cognition. Rather, such liability may reflect a coherent process through which characteristic behavioral traits emerge as a homeostatic response to the way an infant’s brain represents the world. This does not preclude fractionation (e.g., by the degree of influence of different inherited liabilities) but predicts that fractionation at the level of distal causal paths may not necessarily readily map to later symptom profiles.

Such accounts build on a long history of transactional models of developmental psychopathology in which development is shaped by complex interactions between genetic, neurobiological, cognitive, and environmental factors, and view psychiatric symptoms as adaptive responses to an adverse external (or internal) environment (e.g., Frankenhuis & Panchanathan 2011, Johnson et al. 2015b). For the typically developing child, early social interaction provides environmental scaffolding, in which social partners increase the complexity of exchanges as the child’s skills

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grow to maintain a moderate level of contingency on the child’s behavior (Elmlinger et al. 2019). This is akin to progress within a computer game or to the training algorithms within an online chess engine. In typical development, moderate parental contingency and informativeness prompt children to actively seek more social interaction. However, if alterations in the fidelity of early sensory processing or atypical social engagement affects the child’s opportunities to learn about social cues, their understanding of social situations will increasingly lag behind the social level at which society expects them to be. As a result, social situations become progressively less rewarding and the child may progressively exploit other nonsocial niches that better suit their processing style (Johnson et al. 2015b). This unfolding developmental process and the brain state in which it results may ultimately provide a much closer approximation to the latent trait than is afforded by traditional concepts of diagnostic symptom clusters.

Under such models, neurobiological signatures of autism might be expected to be detectable at the whole-brain level, because they are proposed to reflect a coordinated state of the brain that is predisposed by specific profiles of inherited liability. Further, neural signatures of autism-related variation in social behavior would be likely to change over early development as adaptation progresses. Measures of functional brain activity using electroencephalography (EEG) provide converging evidence that neural signatures of autism migrate from sensory regions to the anterior cortex over the first two years of life (e.g., Bosl et al. 2018, Gabard-Durnam et al. 2019). For example, Bosl et al. (2018) applied a machine-learning approach to nonlinear measures of EEG complexity taken from infants aged 3 to 26 months and showed that the features predictive of later ASD were primarily in left temporal and right temporoparietal regions in early infancy and later diverged in frontal regions at approximately 18 months. Importantly, the same machine-learning model that predicted ASD outcome also predicted dimensional variation in autism trait scores within the group as a whole. However, other studies have identified alterations in frontal regions within the first 12 months that are predictive (e.g., in delta and gamma power in infants aged 3 to 12 months; Gabard-Durnam et al. 2019). Replication and assimilation of these approaches to analysis in large cohorts are needed to develop a coherent picture. Deeper understanding may need to rely on methods that allow us to jointly examine changes in brain trajectories and the emergence of autistic behaviors.

The model of a developmental substructure described herein raises the question whether it is even possible to recover neural signatures of causation after autism develops. If not, it would explain why robust diagnostic biomarkers have been challenging to identify, and why biomarkers of clinical affectation may be highly distinct from early biomarkers of risk and causation. To take one example, the N170 is a rapid neural response that is sensitive to faces and is generally accepted to index face expertise. Alterations to the N170 neural response are visible in infants with later ASD (Jones et al. 2016) and also in children and adults with a diagnosis relative to neurotypical controls (Kang et al. 2018), although the experimental results in relation to the latter group are mixed and highly dependent on localization of brain regions in which the signals are recorded (Sysoeva et al. 2018). Notably, biological signatures of causal influences may exhibit stronger covariance with individual differences in behavior among unaffected individuals than among clinically affected subjects. Data from research on identical twins have demonstrated substantially weaker twin-twin correlations among affected subjects than among unaffected subjects, suggesting that impairment at the clinical level may be associated with disruption of usual/expectable relationships between genetic causation and variation-in-severity within the affected group (Castelbaum et al. 2020). This finding is consistent with emerging results from large studies of autism that show clear case-control differences for selected traits that do not necessarily exhibit concomitant dimensional associations within the group with autism (Del Bianco et al. 2020).
Advancing Understanding of the Phenomenon of Canalization in Typical Development

These findings on the erosion of expectable associations between causal factors and variation-in-severity above the clinical threshold invoke the notion that impairment at the clinical level reflects a reduction in the capacity for developmental buffering, or canalization, in the sense that phenotypic development above the clinical threshold becomes both more exaggerated [less constrained within the window of phenotypes that allows adaptive behavior—the norm of reaction (Sarkar 1999)] and more strongly influenced by stochastic and random environmental fluctuations (Castelbaum et al. 2020). Under this model, clinical status may be more likely to be reached when strong inherited liabilities are coupled with the removal or reduction of developmental buffering mechanisms. This finding is consistent with the complete overlap of PGRSs between the affected and nonaffected groups in the Simons Simplex Collection (D’Abate et al. 2019), which suggests that susceptibility to a clinical state of impairment may become amplified beyond the level predicted by inherited liabilities. Such decoupling of liability and outcome might only occur when buffering is removed or when there are high levels of inherited liabilities, pushing the system toward a condition where buffering is required. Moderators that remove a buffering process might not necessarily act additively, as is possible for the role of sex in differentiating the phenotypic expression of a broad array of inherited liabilities to ASD.

What mechanisms are relevant to developmental buffering? As discussed above, development is shaped by a suite of mechanisms, including canalization (which can be conceptualized as the suppression of phenotypic variation between individuals), stability (the suppression of phenotypic variation within an individual), and morphological integration (how variability is structured by the underlying developmental and genetic relation between traits; Hallgrímsson et al. 2002). The idea that these processes are relevant to neurodevelopmental disorders is longstanding—Down syndrome has been interpreted as a syndrome of developmental instability, and fluctuating asymmetries (a sign of developmental instability) have been proposed as risk markers for developmental delay. One important way genetic or environmental extremes can reduce canalization is by producing developmental configurations that have not been selected for canalization. This is potentially why, within animal models, mutant phenotypes are often more variable than wild type (Hermisson & Wagner 2004, Wilkins 2002). Stressful environments also reduce canalization, because they represent environments to which an organism has not adapted. Indeed, stressful environments such as institutionalization have been associated with an elevated risk for both autistic-like behaviors and a broad range of other developmental impacts (Humphreys et al. 2017).

In addition to an altered starting state, in autism there may be direct mutations in the processes that enable canalization itself. Transcription and translation processes have been widely implicated in the genetics of autism (de la Torre-Ubieta et al. 2016), and interactions between transcriptional regulators may play important roles in developmental canalization (Ozbudak et al. 2002, Siegal & Bergman 2002). Gene translation is also an important source of developmental noise (Raser & O’Shea 2005). Related to both sources are epigenetic alterations, which have been implicated as a source of variability between monozygotic twins (Wong et al. 2014) and have begun to be studied in infant populations (Gui et al. 2020a). Buffering can also be considered at the brain network level, particularly in the important role of inhibition/excitation coordination. Inhibition/excitation coordination is important in maintaining homeostatic balance in brain circuits, is intimately related to sensitive periods (Dorrn et al. 2010), and is important for the development of adaptive exploratory behavior (Hellyer et al. 2017). Impairments in inhibition/excitation coordination, possibly linked to disruptions in relevant neurotransmitters [gamma-aminobutyric acid (GABA) or glutamate] (e.g., Horder et al. 2018), have been strongly implicated in ASD (Lee...
et al. 2017). Notably, a shift in the timing of the transition of GABA to its mature function as an inhibitory neurotransmitter has been implicated in ASD and may happen later in males. An excess of excitation may explain a higher prevalence of epilepsy in individuals with ASD. Understanding the nature of disruptions of canalization—particularly any that could be prevented or buffered—may have extremely important implications for intervention approaches aimed at ameliorating the severity of the condition among affected individuals.

**Implications for the Search for Preemptive Interventions Targeting Intermediate Phenotypes**

Elucidation of intermediate phenotypes on the pathways to later ASD may reveal potential intervention targets that relate neither to the genetic substrate level nor directly to the clinical manifestations of ASD when fully expressed as a clinical syndrome. When such interventions are correctly timed in the appropriate developmental window, it may be possible, for example, to enhance aspects of social engagement and social attention via environmental enrichment interventions such as parent-mediated dyadic communication/engagement programs (Landa 2018). Drawing on approaches developed from the broader literature on positive parenting of infants, which uses video feedback to help parents understand and adapt to their infant’s individual communication style to promote social and communicative development (Bakermans-Kranenburg et al. 2003), Green et al. (2015) demonstrated that a 12-week parent-mediated intervention for infants aged 7 to 10 months with an elevated familial likelihood of ASD led to a short-term increase in parental nondirectiveness and (nonsignificantly) infant attentiveness to parent in a pilot randomized controlled trial (RCT). At follow-up, there was an overall reduction in autism traits and an increase in parent nondirectiveness/synchrony and child attentiveness/communication initiation through 36 months of age (Green et al. 2017). However, two RCTs of similar parent-mediated interventions with infants from community samples identified via early ASD behavioral screening measures at 12 months of age have more mixed findings, with Whitehouse et al. (2019) reporting no differences in parenting behavior or in child dyadic communication, and Watson et al. (2017) reporting increases in parental responsiveness but no changes in infants’ early autism symptoms, adaptive functioning, or language. Employing direct electrophysiological and habituation measures of social attention, Jones et al. (2017a) demonstrated that, following a similar 10-week parenting program delivered from 9 to 11 months of age, infants at enhanced familial likelihood of ASD showed changes in neurocognitive measures of social attention (e.g., greater reduction in habituation times to faces versus objects, greater increase in frontal EEG theta power, and greater P400 response to faces versus objects) that resembled, postintervention, those seen in typically developing infants. Future studies that directly couple the effects of direct neurocognitive measures of the candidate intermediate phenotypes that lead to later ASD and the effects of direct measures of emergent autistic traits/symptoms will be important to clarify the mechanisms of effect of such approaches.

In these studies it was not the case that all infants who were recruited between 6 and 12 months of age were on the trajectory to a later ASD presentation; indeed, in the cohorts with an elevated familial likelihood it was likely that only a minority were on such a trajectory. In fact, infants who show the earliest signs of autism in the first year of life are more likely to be severely impaired, many with co-occurring cognitive impairments, a subgroup who may be less responsive to early intervention than asymptomatic infants at increased familial risk. Part of the motivation for initiating such studies was the rationale that targeting the intermediate phenotype of social attention/engagement at a very early but developmentally appropriate point in time might lessen or ameliorate the severity of future autism. A corollary of our proposition that intermediate phenotypes early in development are both shared and influenced by other neurodevelopmental
conditions, and are not specific per se—at least in early development—to ASD, is that preemptive intervention might be targeted toward a broad array of developmental competencies and that appropriate ascertainment of outcome should be broader than a reduction in core symptoms of early ASD. Following this logic, such preemptive interventions are not about preventing autism. These interventions act on transdiagnostic, intermediate neurocognitive/neurobehavioral phenotypes and would be expected to cause shifts in neurodevelopmental, experiential, and adaptive processes that will have much broader downstream neurodevelopmental effects. It is currently unknown whether these approaches or approaches such as those that target another of our intermediate phenotypes—early executive attention—might also impact transdiagnostically the later emergence of common co-occurring traits such as ADHD or anxiety difficulties (Talbott & Miller 2020), although proof-of-concept pilot RCTs with infants at an elevated familial likelihood of ADHD and preterm infants are currently underway (Goodwin et al. 2016, Perra et al. 2020).

To date, these have been mostly small-scale, proof-of-concept studies but the logistic challenges of studying infants at risk and offering universal as opposed to targeted interventions are considerable. Such preemptive intervention approaches also raise some novel but important ethical challenges from the viewpoint of both the infants and the parents involved in the studies. These challenges include the ethics of providing parenting interventions in relation to infants who would have gone on to be typically developing, although the programs are derived from positive parenting approaches that have been implemented with a wide range of samples often with some indicative (infant or parent) risk for adverse outcomes (Juffer et al. 2017). The studies of elevated familial likelihood, many of which have been associated with better-than-expected outcomes for infants under close surveillance within the programs (Micheletti et al. 2020), involve directly engaging in discussions about parenting behaviors and the influence of these behaviors on infants’ developmental progress and outcomes. By design, these studies include families in which there will be enhanced rates of the broader autism phenotype presentation, including in some of the parents themselves. Parents have reported the approach to be a positive experience, giving them an enriched sense of their infant child and increased enjoyment in parent-child interaction, reflecting the generic quality of the positive-parenting approach, which is designed to be adaptable across both typical and atypical development.

**Access to Early Intervention and Support Should Not Be Delayed Due to the Lack of an Autism Spectrum Disorder Diagnosis**

In many communities and clinical practice settings a watch-and-wait principle still holds sway in pediatric services. When a child is seen for a developmental assessment in the first few years of life but the presentation is not clear enough to meet criteria for ASD or another developmental disorder, the parents are advised to come back at a later date, even when the parent has concerns about their child’s development or behavior. Such reassuring or passive responses by practitioners are strongly associated with delays in obtaining an ASD diagnosis, often by many years (Constantino et al. 2020, Zuckerman et al. 2015). Overinsistence on absolute certainty of diagnosis in the early years, when neural plasticity potential might be at its highest, ends up acting as a barrier to whatever services and interventions are available. Conceptually and empirically, early diagnostic challenges are to be expected. At earlier ages there are transdiagnostic perturbations to neurocognitive and behavioral development that are shared in infants and toddlers whose presentation will later resolve to that of a child with ASD, ADHD, language delay, or general developmental delay, alone or in some combination. In other words, the traits that will later lead to ASD in infancy will not be an infant version of the later clinical diagnosis. Watch-and-wait also makes little clinical sense. Two-year-olds with emerging neurodevelopmental disorders struggle to communicate effectively,
and their communication and behavior restricts their opportunities to learn and develop. This impacts their parents, who find their behavior perplexing and challenging to manage. Furthermore, many of the interventions that support children’s communication development and help parents anticipate, regulate, and manage their young child’s behavior will be both needed and of benefit whatever the eventual diagnostic categories the child meets later in their development. Rather than being led by diagnosis, clinical services should offer a stepped approach that matches assessed needs, from broader and more general interventions to increasingly specific interventions, as the child’s neurodevelopmental difficulties (and diagnoses) and profiles of strengths and needs emerge over time (Monteiro et al. 2016).

Individualizing the Approach to Assessing Liability and Early Diagnosis

The data that support the existence of a developmental substructure for ASD have strong implications for clinical developmental assessment. In this framework, a child’s behavior should be viewed as an amalgam of developmental competencies (e.g., general cognition, affect regulation, impulse control, capacity for reciprocal social behavior, verbal and nonverbal communicative ability), in which each competency can be quantified, rather than constraining evaluation to a determination of whether any one competency is abnormal to conform to a unilaterally defined diagnosis. Moreover, the profiles and interactions between those critical developmental competencies have yet to be subjected to standardized characterization (in the same way that clinical implication of a weight measurement is not judged in absolute terms, only in the context of height, and is based on population-normed height versus weight tables). We eagerly await the next generation of developmental-epidemiological studies (some of which are currently underway) that will map the ways quantitative variations in cognition, capacity for reciprocal social behavior, language, attention, emotional regulation, sensorimotor function, and interpersonal experience interact with one another over the course of development, from infancy to adulthood. It is possible that such studies will pave the way for a new system of characterizing syndromes of developmental delay along measurable quantitative axes, each of which might allow more precise associations with contributing neural mechanisms (Constantino 2019). This possibility motivates a call for personalized/individualized medicine approaches to embrace quantification of developmental risk along genetic, behavioral, and environmental axes. Such information will be extremely useful in analyses of intervention studies to better understand moderating and mediators (essentially predictors and mechanisms) of treatment outcomes.

Practical Considerations for Biomarker Discovery

The notion that each occurrence of familial autism represents one of many possible permutations and combinations of independent developmental liabilities of varying but specifiable levels of severity creates new opportunity for personalized approaches to intervention as well as pragmatic guidance for nearly every aspect of biomarker discovery in autism. Relating biomarkers to inheritance and to the developmental liabilities described in this article (recognizing that the heritability of the condition diverges from the causes of its severity) may improve statistical power to identify robust biological signatures of the condition. Biomarkers have been powerful allies in advancing translational research in most branches of medicine, from cancer to hypertension to Alzheimer disease, and for inherited forms of autism the search for biomarkers has thus far proven most productive when focused during infancy, prior to the period when autism emerges. Key examples include total brain (Hazlett et al. 2017) and CSF volume (Shen et al. 2017, 2018), early abnormalities in social visual engagement (Constantino et al. 2017, Jones & Klin 2013), atypical
electrophysiologic recordings, and very recently, CSF vasopressin levels in newborns (Oztan et al. 2020). Of note, effective stratification of biomarkers that identify the biological or developmental correlates of a particular inherited liability may not produce subgroups who meaningfully differ in symptom profiles at the clinical level (because the same symptom profile could result from many other liabilities), but may nonetheless enable targeted treatment that ameliorates symptoms in the subgroup for whom that liability is particularly penetrant. One area that remains to be determined is whether it is possible to identify biomarkers of the latent trait that underpins behavioral symptoms of autism (which we could think of as autism-related variation in reciprocal social behavior). These biomarkers would likely be observed at the whole-brain level (e.g., Hazlett et al. 2017) and, if a latent trait underlying autism represents a developmental process, would be more productively examined by measuring change over early development than at any static point in time.

Furthermore, when studying any aspect of the relationship between genotype and phenotype, or between a putative biomarker and its association with development and behavior, an overarching implication of the developmental substructure described herein is that many typical individuals in the population will have aggregations of one or more trait liabilities that contribute to the development of autism. If so, failure to measure those characteristics among control subjects in case-control research designs will diminish any signal that differentiates groups on the basis of linkage to a specific contributing trait. Therefore, taking stock of predictors of recurrence in autism, as summarized above, and including their ascertainment in the characterization of control subjects should serve as a new priority in the design of biomarker studies. Further, weak but replicable case-control differences should not be discarded; rather, they may provide valuable indications of putative liabilities that could then be entered into multivariate analyses to detect profiles that shift the probabilities of diagnosis with larger effect. A corollary is the possibility that even minor improvements in the severity of a contributing liability could tip the balance of an allostatic load in favor of typical development, perhaps most potently if applied before (not after) the usual time of onset of signs and symptoms of autism. Even if contributing developmental liabilities prove to be secondary to more proximate brain developmental processes, new understanding of the role of nonshared environmental influences offers additional hope for novel strategies to ameliorate the severity of the condition in affected individuals. This may include buffering the effect of stochastic influences on brain and behavioral development, which have long been implicated in psychopathology and for which excess vulnerability may represent a signature of clinical status not only in autism but in other neuropsychiatric disorders.

CONCLUSIONS

Autism is a highly heritable neurodevelopmental disorder that affects the quality of life of millions of individuals worldwide. Despite decades of effort, we understand little about the mechanisms through which genetic risk factors lead to a clinical diagnosis, and there are no licensed treatments for the core symptomatology. In this article we have presented coalescing evidence to suggest that our historical focus on finding specific and necessary factors associated with a categorical diagnosis of autism, and parallel efforts to fractionate the disorder on the basis of its clinical presentation, may have been somewhat misguided. Rather, we present a view of autism as the outcome of a multifactorial process that is prompted by a series of complex interactions between sets of both specific and general inherited liabilities over early development. Such a view sets clear priorities for empirical and clinical progress. Implications for research include increasing focus at early developmental stages, prior to canonical symptom emergence; accelerating work on early transdiagnostic predictors and their relation to a range of neurodevelopmental outcomes; the importance of more complex statistical modeling approaches that incorporate interactions
between multiple predictors; and the need to largely decouple stratification biomarker development from symptom profiles. Clinically, the currently presented view suggests it is imperative that early intervention efforts focus on transdiagnostic domains of functioning that may boost outcomes for all engaged children; strongly argues against watch-and-wait approaches to early support; and raises the important possibility that, compared with typically developing individuals, individuals with autism may be more susceptible to environmental risk factors, which sadly they may also more commonly experience and may be more adversely affected by them. Finally, we note the critical importance of joining forces with researchers studying related neurodevelopmental conditions who may have been looking at the same “elephant” (Saxe 1882, p. 135) from another angle, and with whom we may piece together more of the holistic picture.

**SUMMARY POINTS**

1. Recent studies have highlighted combinatorial effects of independent early-inherited liabilities that may account for both causation and heterogeneity in familial autism.

2. This new body of research suggests the existence of a previously unrecognized developmental substructure for autism in which a finite number of distinct intermediate phenotypes—including, but not necessarily limited to, social visual disengagement, inattention, deficits in predictive modeling, and impairment in motor coordination—contribute additively to a singular latent trait encompassing autism-related variation in human social development.

3. Abnormality at the clinical level in this latent trait is hypothesized to precede and secondarily engender the disparate symptom clusters that characterize the condition: impairment in social communication and restricted interests and repetitive behaviors, which are tightly intercorrelated not only in individuals with autism but also in the general population.

4. If such a substructure underlies inherited forms of autism (which constitute most cases in the population), it has significant scientific implications for linking genes, brain, and behavior in biomarker research and clinical implications for the identification of presymptomatic treatment targets, which would differ from autism symptoms per se, which are the typical focus of intervention after the clinical syndrome emerges.

**FUTURE ISSUES**

1. These data suggest new opportunities to define patterns of liability that distinguish causal origins of autism across different affected individuals and families, and therefore set the stage for personalized approaches to optimizing early treatment and ameliorating the severity of the condition.

2. A next set of priorities involve continued work toward identifying a more complete list of contributing influences and understanding how inherited liabilities operate together to incur risk for autism, as well as mapping the interactions between inherited polygenic susceptibility, penetrant de novo variants, and environmental adversity in the accumulation of risk for clinical autistic syndromes. Greater understanding of the
mechanisms by which additive early liabilities converge on a singular latent trait will advance knowledge of the phenomenon of canalization, which characterizes typical developmental trajectories and is believed to be qualitatively disrupted in enduring syndromes of atypical brain and behavioral development.

3. A next translational step is to determine whether ameliorating the impact of any one contributing liability in infancy might tip the balance of an allostatic load in favor of typical development, perhaps most potently if applied before (not after) the usual time of onset of signs and symptoms of autism. The data reviewed here suggest that for young children at an elevated risk for or showing early signs of the condition, access to early intervention and support should not be delayed due to the lack of a definitive autism diagnosis.

4. Recently identified candidates for early neural signatures of autism, detectable in the first year of life through advanced neuroimaging and electrophysiologic technologies, can be explored in tandem with behaviorally defined developmental liabilities whose detection in larger studies has principally driven the reconceptualization described in this article. A distinct goal is to determine the extent to which they map to one another or, rather, to highlight independent parameters of risk that may complement measurable behavioral liabilities to allow for an even higher level of risk prediction.

5. Future forays into biomarker research, including neuroimaging and genotype-phenotype association studies of autism, must recognize that control subjects possess quantitative, subclinical aggregations of the same causal liabilities that contribute to autism. Therefore, optimizing statistical power to elucidate signatures of the disorder may depend on phenotypic ascertainment of these same liabilities in both cases and controls.

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Errata

An online log of corrections to *Annual Review of Clinical Psychology* articles may be found at http://www.annualreviews.org/errata/clinpsy