

## Regular Article

# Affording autism an early brain development re-definition

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### Abstract

The national priority to advance early detection and intervention for children with autism spectrum disorder (ASD) has not reduced the late age of ASD diagnosis in the US over several consecutive Centers for Disease Control and Prevention (CDC) surveillance cohorts, with traditionally under-served populations accessing diagnosis later still. In this review, we explore a potential perceptual barrier to this enterprise which views ASD in terms that are contradicted by current science, and which may have its origins in the current definition of the condition and in its historical associations. To address this perceptual barrier, we propose a re-definition of ASD in early brain development terms, with a view to revisit the world of opportunities afforded by current science to optimize children's outcomes despite the risks that they are born with. This view is presented here to counter outdated notions that potentially devastating disability is determined the moment a child is born, and that these burdens are inevitable, with opportunities for improvement being constrained to only alleviation of symptoms or limited improvements in adaptive skills. The impetus for this piece is the concern that such views of complex neurodevelopmental conditions, such as ASD, can become self-fulfilling science and policy, in ways that are diametrically opposed to what we currently know, and are learning every day, of how genetic risk becomes, or not, instantiated as lifetime disabilities.

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### Perceptual Barriers to Early Identification and Treatment of Infants and Toddlers at Risk for ASD

For the past decade, a strong consensus has emerged among the scientific community singling out early detection and intervention as critically important factors in societal efforts to optimize outcomes of children with autism spectrum disorder (ASD) (Daniels, Halladay, Shih, Elder, & Dawson, 2014; Dawson, 2016; Dawson et al., 2010; Dawson & Bernier, 2013; Reichow, Barton, Boyd, & Hume, 2012; Warren et al., 2011; Wetherby et al., 2014). And yet, the median age of ASD diagnosis in the US remains stubbornly stuck at the late age of 4–5 years (Baio et al., 2018; Christensen et al., 2016; Maenner et al., 2020), and later still in low-income families (Christensen et al., 2016; Fountain, King, & Bearman, 2011; Mandell et al., 2009). Although community uptake of universal screening for ASD in primary care appears to be steadily rising (Adams & Tapia, 2013; Daniels et al., 2014), several challenges continue to limit the beneficial impact of this practice, including screening tools with unacceptable levels of false negatives (Guthrie et al., 2019), indications that approximately half of all screen-positive children may never access diagnostic services (Daniels et al., 2014; Robins et al., 2014), and a pervasive belief by some practitioners that no definitive evidence is available to date proving that universal

screening efforts lead to better outcomes, a belief that may deeply undermine efforts to implement universal surveillance and screening practices (Al-Qabandi, Gorter, & Rosenbaum, 2011; Siu et al., 2016). Collectively, these challenges greatly restrict access to federally mandated early treatment, 34 years after the original mandate was created as Part H of the Individuals with Disabilities Education Act (IDEA), and 23 years after it was re-authorized by US Congress as Part C of IDEA (Adams & Tapia, 2013; US Department of Education, 2018).

This entrenched public health failure remains unchanged over the years despite the high priority assigned to ASD early detection and treatment by some leading scientific and professional organizations, such as the Interagency Autism Coordinating Committee (IACC) (US Department of Health & Human Services, 2017) and the American Academy of Pediatrics (AAP) (Hyman, Levy, & Myers, 2020; Johnson & Myers, 2007). The IACC coalesces the expertise and resolve of all federal agencies involved in ASD research and services, including the National Institutes of Health, while the AAP has, since 2007, made universal screening for ASD a key element of their recommended best practices. These recommendations, however, have not translated into binding policies, data-monitored practices or societal investments commensurate with the level of criticality assigned by these leading organizations to early detection and intervention. Consider, for example, that the IDEA Part C—as noted, the portion of the IDEA focused on infants and toddlers with disabilities—receives only 3.5% of the entire US\$13.45 billion IDEA appropriation, with 95% of IDEA funds dedicated to education of children aged 3–21 years (Dragoo, 2019). While one important appropriation purpose should not come at the expense of another, this

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distribution highlights the fact that the period of birth-to-three years is undervalued in societal efforts to address the needs of children with developmental disabilities. It is no surprise, therefore, that among children with neurodevelopmental conditions, only 20% of those who receive special education services during their school-age years are identified prior to the age of 3 years (US Department of Education, 2018).

These realities are completely unaligned with research. Scientific evidence continues to accumulate, indicating that the earlier a child's diagnosis can be established, the better the child's long-term outcome and the less expensive and intensive services need to be later in the child's life (Dawson et al., 2010; Reichow et al., 2012; Warren et al., 2011; Wetherby et al., 2014). In summary, *our current societal investments reflect a major disconnect between science and policy, undoing the public health opportunities afforded by early treatment*: we are neither optimizing outcomes nor being good stewards of limited governmental funds. In fact, most of the federal resources available to benefit individuals with ASD and their families go to provide educational, medical and support services to severely affected adolescents and adults with ASD (Buescher et al., 2014; US Department of Education, 2018). While this is, of course, a critically important need, this allocation seems to be self-perpetuating because of a widely held view that the severely compromised outcomes of some children with ASD is an inevitability. At times, it appears that for some stakeholders, ASD is this profile of severely compromised outcomes, and this view can, and it maybe has, become a self-fulfilling policy. It can hamstring the movement that advances the opposite outlook, namely that future outcomes of children with ASD, and the political economy of ASD, can be radically improved via greater community uptake of effective surveillance and screening methods, and of increased access to diagnostic services and to cost-effective early treatments.

For developmental scientists, the essence of the argument is clear: due to delays in early detection and treatment, the point at which a child can be accurately identified and treated moves from within a window of tremendous neuroplasticity (Johnson, 1999)—the first months and years after birth—to a point several years hence, when many years of development have already interceded and played a large role in shaping the course of a child's condition (Klin, Jones, Schultz, & Volkmar, 2003). This marks the loss of a potentially critical opportunity for improving treatment efficacy and associated outcomes (Dawson et al., 2012). From a public health standpoint, the effects of this failure are equally clear: because of late detection and diagnosis, at least 50% of children are identified only during their school-age years, often, by then, because of severe disruptive behavior and aggravated social, communicative, and behavioral symptoms resulting from years of untreated ASD (Klin & Jones, 2018). And because age of detection and diagnosis is later still in low-income, minority, and rural populations, children with ASD in these sectors of the community may have worse outcomes than those of their middle-class/Caucasian peers (Daniels & Mandell, 2014) as a direct result of this healthcare disparity. The latest Centers for Disease Control and Prevention (CDC) ASD prevalence data support this hypothesis: by the time children with ASD are 8 years old, the burden of intellectual disability among African American children with ASD is 47%, or almost *double* the burden of intellectual disability in Caucasian children, which is 27%; for Hispanic children, the rate of intellectual disability is 36%, falling between these two extremes (Constantino et al., *in press*; Maenner et al., 2020).

Factors hindering population-wide uptake of early detection and intervention can be traced to a wide range of implementation challenges, such as lack of cost-effective and accurate screening tools, challenging time requirements and lack of cost coverage in primary care settings, limited funding for and integration of family supports, among others (Daniels & Mandell, 2014; Guthrie et al., 2019; Honigfeld, Chandhok, & Spiegelman, 2012). Solutions for each of these obstacles will advance implementation of early detection and intervention, but they will not counter an obstacle of a different kind—a *perceptual barrier*, a prevailing view of ASD, held by many scientists, providers, and policy makers alike, which undermines any discourse advancing the potential benefits of early treatment. We raise this hypothesized challenge because we have encountered it consistently in scientific and policy/advocacy forums, among colleagues in research centers, and in policy-making and execution agencies. It refers to a view of ASD that sees the condition as a relatively rare brain “disease” of genetic origins, defined by intellectual disabilities and severe behavior challenges, and with lifetime outcomes defined primarily by deterministic gene–brain pathology a child is born with. This view of ASD has two main implications. First, it prompts a science intended to find “the cause” of ASD and to generate a treatment for it, with the ultimate goal of “curing” individuals of this “disease.” Second, it limits our imagination, and our resolve, to consider the possibilities afforded by early treatment given that, according to this view, the potential for change and improvements are deterministically constrained by the genetic and brain liabilities a child is born with. We pose that this is a limiting and untenable view of ASD; that it originates from the current definition of ASD, and from its historical roots; and that it is contradicted by new research emerging in genetics, epidemiology, and developmental social neuroscience. We pose further that in order to recover the world of possibilities afforded by this new science, there is a need to ground ASD research and policy, certainly insofar as infants and toddlers are concerned, in a developmental psychopathology framework (Beauchaine, Constantino, & Hayden, 2018). In essence, we need to afford ASD of an early brain development re-definition.

To present an early brain development rethinking of ASD in juxtaposition to a view of ASD as a “rare genetic disease” might appear to some as a “strawman argument”: most investigators in the field would not subscribe to the notion that ASD is either “rare” or “immutable.” Our intention in using this juxtaposition is to lay bare the possibility that even though few would subscribe to this notion, many construct their hypotheses, design their experiments, and interpret their findings in ways that perpetuate it, thus leading to waves of science and policy debates consistent with the logical implications of this outdated view. In many ways, this situation is consistent with what Oyama (2000) masterfully described as the nature/nurture false dichotomy, as most investigators do not openly espouse a radical nature-only or nurture-only approach and yet appear to create theories and build experiments to test them as if they did. Most importantly, such tendentious lines of research are likely to perpetuate the false dichotomy and to fail to advance more sophisticated syntheses capable of moving the field of child development forward (Oyama, 2000).

### The Current Definition of Autism Spectrum Disorder (ASD) and its Misconceptions

The definition of ASD remains essentially unchanged since Kanner's observations of 11 children who displayed a

constellation of behavioral symptoms in the areas of social and communicative function, behavioral rigidities and sensory sensitivities (Kanner, 1943). Rutter codified these symptoms (Rutter, 1978) in what became eventually the formal nosology of autism (Volkmar, Bregman, Cohen, & Cicchetti, 1988), enduring, with minor changes, to this day (American Psychiatric Association, 2013; Lord & Jones, 2012). There have been, nevertheless, dramatic advances in the operationalization of the definition (Lord et al., 2012), both in terms of standard tools for diagnosis (Kim & Lord, 2012) and a broadening of phenotypic expressions to encompass individuals with lesser levels of syndrome expression and disability (Lord & Jones, 2012). In fact, it became one of the most well-researched and validated nosologic entities among all psychiatric conditions, and it has made possible the emergence of a massive scientific literature, more accurate prevalence rates, and the critically important attainment of life-changing medical, educational, and support services for individuals with ASD (Silverman, 2012; Volkmar & McPartland, 2014).

For all of the remarkable achievements of the categorical definition of ASD, its enduring continuity over decades also resulted in the accumulation of cultural and scientific perceptions that no longer apply. These perceptions come from some preservation of obsolete knowledge and from some failure to assimilate the implications of new knowledge. Consider that what we know now is vastly different from what we knew at the time the term “autism” was coalescing into a set of observational criteria, around the late 1960s and 1970s: prevalence was thought to be 4:10,000 (Wing, O’Connor, & Lotter, 1967)—not the current 185:10,000 (Maenner et al., 2020); the rate of intellectual disabilities was thought to be up to 80% (Rutter, Greenfeld, & Lockyer, 1967)—not the current epidemiological rate of 33% (Maenner et al., 2020); its genetic basis was suspected but was otherwise a mystery (Rutter, 1968)—now we know of over a hundred genes implicated (Satterstrom et al., 2020) and a recurrence rate in sibships of 16–36% (McDonald et al., 2019), with another considerable percentage displaying subthreshold forms of the condition (Ozonoff et al., 2011); and while both Kanner and Rutter surmised that autism was present from birth, there was no, or very little, direct observations of the first three years of life (Klin et al., 2004); now knowledge of prodromal expressions is accruing at a very fast rate (Szatmari et al., 2016), and brain–behavior developmental trajectories of infants later diagnosed with autism are being charted almost from birth (Hazlett et al., 2017; Jones & Klin, 2013).

These straightforward historical contrasts should influence our views of what ASD is and is not. ASD is amongst the most common complex neurodevelopmental conditions; it is not a syndrome of intellectual disabilities. Its genetic basis is extremely complex, with literally hundreds of etiologies. Heritability is very high but it shades into a spectrum of clinically subthreshold expressions, including expressions that could be described as normally distributed human traits rather than symptoms (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010); and the emergence of symptoms by the second and third year of life, the very symptoms that define the condition, is the *culmination* of a developmental process that begins from birth or shortly thereafter, not its onset (Johnson et al., 2005; Shultz, Klin, & Jones, 2018).

#### *Consider the implications of not assimilating these facts into our views of ASD*

If the psychiatric category of ASD delineates a well-defined and discrete pathological condition, set as a binary nosology of ASD

versus non-ASD (like having or not having an infection), and if ASD is viewed as a rare and an almost invariably devastating cause of impairments to a child’s intellectual and adaptive skills (like a monogenic and highly penetrant genetic syndrome such as Rett syndrome; Lyst & Bird, 2015), then it should be no surprise that such a condition would be treated as other serious low-prevalence medical diseases of genetic origins (like a leukodystrophy). That its science should strive to find discrete causes and discrete treatments (like an antibiotic for a given infection) and that, until causes were discovered and specific treatments were developed, treatments available would be considered limited to symptomatic improvements or to alleviation of suffering. The corollary of this view is also quite straightforward: why should one invest in the early detection of a disease if one cannot cure it or ameliorate it in any substantial way? In fact, investment in early detection and diagnosis might be considered even unethical: why should we screen for a condition for which we have nothing, or nothing curative, to offer?

#### *Now consider the implications of allowing these facts to re-shape our views of ASD*

If the category of ASD is porous and shades into traits rather than pathologies (as in the construct of the “broader autism phenotype” (Sucksmith, Roth, & Hoekstra, 2011); if ASD is common and levels of ability and disability contain the full spectrum of intellectual variation; if genetic risks and heritability patterns are not deterministic of outcome (they are complex and multifactorial, evident in the case of siblings, who may share genetic risks but may be, *or not*, “affected”); and if deviations from normative development precede the onset of symptoms (like high blood pressure may precede a stroke); it should be no surprise that such a condition would be treated as a *common medical risk of genetic origins*—a public health risk rather than a rare disease. This would be akin to the difference between say prematurity and leukodystrophies. Conceptually, it would open up the possibility that whether or not risk converts into a lifetime of disabilities might be a function of interactions between Risk × Early-life events, including not only naturally occurring Gene × Environment interactions but also deliberate, early therapeutic manipulations, which, of course, would only be made possible via early surveillance, detection, and intervention. In this view, science should strive to understand the interplay between genetic risks and disruptions of normative processes preceding the emergence of symptoms, and treatments should be developed to optimize outcomes, by either normalizing experience or by introducing compensatory learning (Zwaigenbaum et al., 2015). The corollaries of this view are straightforward: there is no need to wait for discoveries of what causes ASD or for “cures” to treat the condition because early treatment might promote best outcomes given a child’s inborn risks; these best outcomes are unlikely to mean the erasure of a genetic trait or constellation of traits (like “autism,” or social ability/disability), but the prevention, or amelioration, of associated burdens such as intellectual, language communication or behavioral disabilities (Micheletti et al., 2020). In this light, the lack of investment in early detection and diagnosis is profoundly unethical since whether or not inborn risks convert into a lifetime of disability is dependent on what happens to the child’s early life, and this, in turn, can be intervened with via early treatment. More starkly, one might consider the public health challenge and the public health opportunity associated with ASD: approximately 71,800 children who are

born every year in the US will develop ASD; their lifetime outcomes may depend, to a meaningful degree, on whether or not these children and their families can access early treatment.

This general scientific approach to adverse outcomes resulting from inborn or early-life risks is hardly novel in developmental psychopathology (Cicchetti & Toth, 2009), and it has become deeply ingrained in best-practice parameters, policy, and programs in regards to some conditions such as congenital hearing impairment (Korver et al., 2017); congenital heart disease necessitating first-year-of-life surgery(ies) (Marino et al., 2012; Mussatto et al., 2017); extreme prematurity (Greene & Patra, 2016; McManus, Carle, & Poehlmann, 2012); adverse social and family-related conditions collectively captured by the term “social determinants of health” (Alley, Asomugha, Conway, & Sanghavi, 2016; McGinnis, Williams-Russo, & Knickman, 2002); among many other conditions. The connection works in the other direction as well. Risks for adverse conditions identified in adolescence often originate in early life, with a stark example being juvenile delinquency: to single a critical one—language vulnerability—close to half of adolescents involved in the juvenile justice system present with language disorders (Hughes et al., 2017; Moncrieff, Miller, & Hill, 2018); given the stability of core language skills from infancy to adolescence in typical and atypical development (Bornstein, Hahn, Putnick, & Pearson, 2018), there is consensus on promoting language resiliency in at-risk infants and toddlers growing up in adverse environmental conditions (Johnson, Riis, & Noble, 2016).

*In ASD, by contrasting these two views—autism as a genetic disease relative to autism as a genetic risk—different sets of priorities for future research and policy emerge*

The view of ASD as a genetic disease places it in the company of rare genetic syndromes that may overlap somewhat with ASD in clinical presentation, such as Rett’s syndrome, tuberous sclerosis complex, and Angelman’s syndrome, among others (Richards, Jones, Groves, Moss, & Oliver, 2015), and whose potential for optimized outcomes is more limited given the penetrance of the genetic cause and the severity of its effects. These conditions, in turn, are sometimes deemed so severe that they are discussed alongside potentially lethal genetic diseases, such as spinal muscular atrophy (Kraszewski et al., 2018), in which the scientific imperative is to identify mechanistic processes via which specific mutations lead to disease (i.e., studies to elucidate the causative processes tying molecular abnormalities to abnormal cell and brain circuit pathophysiologies), and then implement a form of gene therapy that can reverse the condition (Dunbar et al., 2018).

The view of ASD as a genetic risk takes us in a very different direction. It begins with a shift in scientific emphasis from causes of neurodevelopmental liabilities to prevention, or at least attenuation, of the deleterious effects of those risks upon early brain development (Klin & Jones, 2018). This is a radical move, and one that takes us away from the prevailing model in investigative medicine, one of the reasons why, we believe, it has had little traction so far. Making the differences explicit might be helpful. This is a move away from the model that has led to some of the greatest achievements in medicine, in which the most momentous health benefits originated from discoveries of causes of disease. Maybe the greatest medical achievement of all, the discovery of germs, led to antiseptic practices in surgical procedures, the discovery of antibiotics, and the development of vaccines, thus preventing or treating lethal infections and providing active acquired

immunity to a host of devastating diseases among millions of people (Butler, 2014; Lewis, 2013; Zaffiri, Gardner, & Toledo-Pereyra, 2012). This influential model, however, has not been fruitful in the management of complex neurodevelopmental conditions. On the one hand, there are several neurodevelopmental conditions for which the causes have been known for several decades and yet our ability to minimize their impact on brain development is still limited. Examples are Fragile X (Warren, Zhang, Licameli, & Peters, 1987) and Rett (Zoghbi et al., 1999) syndromes. On the other hand, for the vast majority of “non-syndromic” affected individuals, the causes of common neurodevelopmental conditions such as ASD (Geschwind, 2011), language and communication delays (Sriganesh & Joseph Ponniah, 2018), and attention-deficit hyperactivity disorder (ADHD) (Thapar, 2018) are extremely complex in their genetic bases and vastly heterogeneous in their symptomatic presentation, thus tempering hopes for momentous etiologic discoveries in the near future that could tractably pinpoint specific, mechanistic and curative treatments to these conditions, as they likely result from multifactorial, early disruptions at the level of molecular, cell and brain circuitry, beginning prenatally, and progressing via cycles of iterative interactions with environment. Most importantly, there is also substantial genetic overlaps between these conditions (e.g., ASD and ADHD), and genetic correlations with a much broader group of neuropsychiatric disorders (Thapar, 2018) and nonpsychiatric conditions (e.g., congenital heart disease) (Homsy et al., 2015).

To shift our scientific focus from “curing a disease” to “optimizing outcomes” does not mean to abandon research on the etiologic bases of complex neurodevelopmental disorders. Rather it calls for near-term action that can promote early brain development despite the burdens with which, or within which, a child is born. This shift may also reflect an emerging realization that common neurodevelopmental conditions, such as ASD and ADHD, are extreme ends of continuously distributed dimensions, akin to hypertension along the continuum of blood pressure (Constantino, 2011; Thapar, 2018). In other words: while usefully conceptualized as disorders in clinical practice, ASD and ADHD can be viewed as constellation of traits capable of adversely impacting development, which is a conceptualization of psychiatric disorders that may also promote greater inclusion of, and less stigma to, individuals affected. In ASD, intellectually intact self-advocates take issue with the definition of their condition as a “disease” in need of curative treatment or prevention, as success in these efforts (say, via gene therapy) would result in the “eradication” of individuals like them; clearly, a more apt and inclusive approach, would be to refer to individuals with ASD as “uniquely human” (Prizant, 2015), with maybe uncommon profiles of trait variation but capable of both attaining unique achievements and of being agents of society’s full load of rights and responsibilities. If the goal of interventions is to optimize outcomes, then the purpose of treatment and supports would not be to “cure a person of a human trait or constellation of traits,” but to ensure that inborn risks or vulnerabilities do not translate into disabilities, specifically, severe intellectual, language and behavioral disabilities.

To shift the focus from an attempt to “cure” ASD to a focus on optimizing the outcomes of children at risk for ASD also expands the realm of inquiry, from specific genetic risks to a more comprehensive view of factors that may promote or compromise a child’s outcome, thus going beyond genetic susceptibility to include a wide range of factors such as adverse medical or environmental conditions, or even random environmental variation (White,

2019). A helpful analogy might be drawn from the field of global health: consider the possibility of not waiting for discoveries of the causes of poverty to begin acting upon the active ingredients that translate poverty into compromised childhood health. For example, while we discuss the roots of poverty, we should not discard the tremendous benefits of immediate action focused on finding say clear sources of drinking water, supplying mosquito nets, and changing policy promoting more favorable social determinants of health. These health-promoting factors are not meant to combat poverty per se, an economics construct; they are intended to promote resiliency, in the presence of the identified risk (being poor), so that a given child is less likely to succumb to a disease or to another adverse outcome that poverty may lead to. More specifically, this approach is meant to identify the immediate, proximal active ingredients (say lack of clean water) of a potentially deleterious influence (poverty). If we apply this analogy to ASD, then the question remains as to what are the potential active ingredients promoting or disrupting early brain development, and whether we can engineer viable solutions—treatments, interventions—that will make vulnerable children—born with genetic risks for ASD—less likely to succumb to their risks—to have ASD with severe intellectual, language, and behavioral disabilities.

It is an interesting question in the history and sociology of medicine as to why ASD has become imbued with this level of genetic determinism while other childhood conditions, such as ADHD, are more readily situated at the intersection of genetics and environment (Faraone et al., 2015). While this may be due to its strong genetics, its early onset, or the public face of ASD as its most severe expressions, this perception may have also been inherent in the history of autism research going back to soon after Kanner's original description (1943). During the 1950s and 1960s, autism was often described in the medical literature as a "psychogenic" disorder, due to "bad parenting": the so-called "refrigerator mother" hypothesis. This perception, with no evidence, permeated public discourse and psychological research, and shaped treatment parameters and even educational policies which, collectively, victimized parents of children with ASD, misled contemporaneous research and clinical practice, and, in some quarters of the world, continued to do so into the new millennium (Grinker, 2007; Silverman, 2012). It is hardly surprising that the first dents into this theory came from parent-scientists of children with autism (Rimland, 1964; Wing, 1969), whose science, including epidemiology, were clearly incompatible with the psychogenic hypothesis. With the advent of the very first twin study of autism (Folstein & Rutter, 1977), the genetic basis of the condition was firmly established, situating autism research strongly in the realm of biological medicine while jump-starting several decades of ever-accelerating advances in genetics research of ASD. One possibility, therefore, for current views of ASD in genetic-deterministic terms might be the residual trauma in the field resulting from the psychogenic hypothesis, a hypothesis that is fully undermined by inborn genetic causes.

Understanding as it might be given this historical context, the perception of ASD in genetic-deterministic terms can itself lead to deleterious effects on research and policy, including efforts to reduce age of diagnosis and increase access to early treatment and intervention. This reckoning is, in our view, overdue. To rephrase the all-important question: what can we do to ensure that a genetic risk (or risks), such as autism, does not convert into a lifetime of disabilities? Two recent debates should benchmark what is at stake if we ignore this issue, thus failing to invest

in research and policy aimed at optimizing the outcomes of vulnerable children.

First, following up on reports that by the age of 24 to 36 months the clinical outcomes of toddlers in research studies depends on a given study's ascertainment strategy (i.e., sampling method; Bornstein, Jager, & Putnick, 2013), a recent meta-analysis compared toddlers' outcomes across studies recruiting subjects prospectively, via community or clinical referral, and via universal screening (Micheletti et al., 2019). The rationale for these comparisons was that if community or clinical referral systematically biases recruitment toward a more severely affected sample, then recruitment using universal screening, without such referral bias, would result in a less severely affected sample, like in the case of prospective recruitment. Results showed that outcomes in community referral and universal screening were comparable, whereas outcomes of children followed prospectively were significantly better. The authors suggested the possibility of a "surveillance effect," or the notion that monitoring and supporting a family prospectively may be by itself a beneficial intervention that, if deployed early enough, might be sufficient to "move the needle" of improved outcomes in young children with ASD. This hypothesis raises the possibility that something as genetically based and potentially grave as ASD could in fact be altered by an effort to train and support caregivers and promote a family's resiliency. If corroborated, surveillance and parent training could become a community-viable intervention. In fact, this possibility would build strongly from evidence-based ASD early treatments, most of which emphasize caregiver-mediated treatments (Schreibman et al., 2015).

And second, the belief of ASD as a deterministic, genetically based disease or disorder, has also resulted in a state of literature that almost virtually ignores the possibility that socio-demographic variables, and early childhood and family hardships associated with these variables, could play a role in determining the outcomes of children vulnerable to ASD (Bornstein et al., 2013; Micheletti et al., 2020). One rarely hears of debates on healthcare disparities, adverse childhood experiences, or social determinants of health in the cases of children with very rare genetic diseases, such as leukodystrophies and highly penetrant genetic syndromes of intellectual disabilities. If ASD is one of such rare and devastating conditions, there should be no need, for example, for NIH or peer-review journals to demand that experimental variables (in clinical science and trials) are analyzed by variables such as socioeconomic status (SES) or race/ethnicity. Of course, such a characterization of ASD is false. ASD research and service are plagued by healthcare disparities, particularly in regards to early outcomes (Daniels & Mandell, 2014), with unacceptable liabilities experienced by some sectors of the community (e.g., as noted, African American children with ASD having almost double the rate of intellectual disability than their Caucasian peers by 8 years of age) (Maenner et al., 2020). And yet, with the exception of some noteworthy journals, it is rare for developmental science studies to include sociodemographic variables (Bornstein et al., 2013). As a result, the question as to whether ASD vulnerability may aggravate and be aggravated by adverse experiences associated with specific socio-demographic variables such as "low-income," "minority," or "rural," and related hardships such as adverse childhood experiences, is virtually untouched in ASD research. And yet, this is precisely the pillar upon which most research in common early childhood conditions is built, conceptually, clinically, methodologically, and epidemiologically (Shonkoff, 2011, 2017). In a way, to consider ASD within

the context of what promotes, or not, early brain development is to tear it away from the “rare disease” class of childhood conditions and place it squarely into the category of “common public health risk.” To draw this analogy more starkly: it is not inevitable that a maltreated infant will end up becoming a juvenile delinquent (Cicchetti, 2013). Similarly, it is not inevitable that an infant born with autism as a risk will end up with severe intellectual, language, and behavioral disabilities (Klin & Jones, 2018).

To define ASD as a genetic risk impacting early brain development makes it akin to a host of other common conditions of early childhood, such as language and communication delays, disorders of attention, learning and self-regulation, among others, all of which have a (complex) genetic component but which are also influenced by a host of environmental factors, collectively pushing and pulling on active ingredients influencing a child’s eventual outcome. To identify these “active ingredients” there is a need to ground ASD in the early-onset normative processes of social and communicative development, and then to interrogate these processes in search of opportunities for promoting resiliency, course corrections, and compensations, all of which integral elements of the developmental psychopathology movement (Cicchetti & Cohen, 1995). In what follows, we briefly survey the opportunities emerging from such an attempt to re-define ASD in terms of early brain development principles and processes.

## Re-defining ASD in Early Brain Development Terms

*A discussion of ASD pathogenesis in the context of early brain development has commonly built on the following themes*

### *On neuroplasticity*

The first two years of human life represent the period of greatest brain transformation: a newborn’s brain doubles in size in the first year of life, and will increase again by another 35% by year three (Gilmore et al., 2007; Pfefferbaum et al., 1994); synaptic density quadruples within year one alone, and will reach levels 200–300% greater than that of an adult by the end of the third year (with concurrent and subsequent pruning and strengthening) (Huttenlocher, 1979; Petanjek et al., 2011). Of importance, longitudinal gene expression associated with synaptogenesis over the first two years of life, over a wide range of brain structures, is characterized by lifetime maximal values across the 6- to 12-month window, then decreases drastically after 15 months, or much before the time at which autism symptoms emerge and the condition can be reliably diagnosed (Kang et al., 2011; Shultz et al., 2018).

In this light, a healthcare system designed to deliver treatment only after an ASD diagnosis is secured, even if the diagnosis is obtained relatively early between ages 2 and 3 years, would already have missed the best window of opportunity signified by this early period of maximal neuroplasticity. It follows that there will be a need for early intervention to be deployed on the basis of prodromal risks, unlikely to be symptoms themselves (aberrant behavior), and more likely to be deviations from normative developmental processes (Klin, Shultz, & Jones, 2015).

A critical aspect of this hyper-neuroplastic period is that brain development is not only being guided by an inborn genetic timetable for maturation, but it is also becoming the physical instantiation of the child’s lived experiences, which in turn, moderate epigenetic processes (Shultz et al., 2018; Szyf & Bick, 2013). This principle of early brain development was stated best in

Joseph Ledoux’s subtitle for his “*Synaptic Self*” book: “How our brains become who we are” (LeDoux, 2003). This principle has two critical implications.

First, a child’s early experiences matter a great deal, contributing to the canalization of subsequent learning, typical or atypical, as experiences result from adaptation and learning and then become the affordance for new learning and experiences, and again and again, in a brain–behavior tight system of interdependence and co-opting movement forward (Fox, Levitt, & Nelson, 2010). Second, this experience and learning is happening in the context of the surrounding environment, via brain-mediated, bi-directional and iterative relationships between a child and their social and physical environments, which need to be rigorously quantified, spatially (in terms of proximity to a child’s internal state, actions, and reactions), and temporally (in terms of time varying periods of a child’s development) (Berman, Stier, & Akcelik, 2019). We know that brain capitalizes on chance events, or stochastic processes, prenatally and postnatally (Jensen, 1997; Molenaar, Boomsma, & Dolan, 1993), and there is evidence that fostering positive environmental factors building on these stochastic processes can optimize neurodevelopment providing a child with greater resilience (White, 2019).

### *On social development and disruptions thereof*

The most robust markers for early diagnosis of ASD in the first 3 years of life include reduced interaction with and attention to others; reduced attention to others’ eyes; failure to respond to the calling of one’s own name; and inability to join in imitative games and reciprocal vocalizations (Klin et al., 2015; Wetherby et al., 2004; Zwaigenbaum et al., 2009)—all failures in normative skills that represent milestones in typical development. These deviations in social interaction and social communication then become causative factors in subsequent atypical developmental, following a trajectory that culminates with the emergence of autistic symptomatology (Klin et al., 2003). Given the centrality and robustness of these early indicators, a great deal of work on the early pathogenesis of ASD has focused on the social and social communication domains of development, with important advancements in quantitative, performance-based assays. This emphasis does not ignore or invalidate research focused on other early signs of ASD, including “domain general” motor, sensory or other early impairments: these may act in concert to generate the defining social–communicative disability in ASD, either via independent and additive genetic liabilities (Pohl et al., 2019) or via developmental inter-dependencies, as most social–communicative competencies require the coordination of skills across various areas of sensory, motor, and cognitive skills (Shultz et al., 2018).

In the social domain, two decades of work have led to the hypothesis that developmental disruptions of evolutionarily highly conserved and developmentally early-emerging mechanisms of socialization drive pathogenesis and result in autism symptoms (Johnson et al., 2005; Klin et al., 2015). These include a wide range of social visual engagement behaviors, such as preferential attention to biological motion (Klin, Lin, Gorrindo, Ramsay, & Jones, 2009), which is not only a “life or con-specific detector” but is also a foundational underpinning of social cognition (Johnson, 2006); eye-looking and gaze behavior (Jones & Klin, 2013), which are critical for extraction of social adaptive information (Kampe, Frith, Dolan, & Frith, 2001), and are potent enhancers of neural processing of social information throughout the lifespan (Adolphs et al., 2005; Farroni, Johnson, & Csibra,

2004); monitoring of social activity (Chawarska, Macari, & Shic, 2013; Shic, Bradshaw, Klin, Scassellati, & Chawarska, 2011), which is critical for detecting the relative salience of specific environmental components and then behaviorally adjusting to them; among others. All of these disruptions in normative skills occur much prior to the advent of ASD symptoms, and some can predict not only diagnostic classification but also level of autistic disability some several years later, when the diagnosis of ASD is already strongly stable (Jones & Klin, 2013).

#### *On the accrual of moment-by-moment deviations from normative social development*

The mechanisms of socialization surveyed above represent tools for moment-by-moment learning that a baby deploys to adapt to the surrounding environment, both physical and social. To fully appreciate the impact on development that disruptions in these mechanisms may have, it is important to restate and emphasize that these are tools for learning and adaptation. Consider social visual engagement, which is the way in which infants visually explore, engage, and ultimately learn from and adapt to their surrounding world. In this domain, genetic control is exercised over macroscales—for example, patterns of visual fixation over minutes of social visual experiences; and over microscales—for example, moment-by-moment predispositions to react to and seek social information in the surrounding social world, such as when to shift one's visual attention, in which direction, and onto which targets, measured in milliseconds (Constantino et al., 2017). In essence, via these predispositions, infants and toddlers create their own individual niches (Oyama, 2000; Super & Harkness, 1986), which both constrain the environmental realm within which they will learn, and intensify inter-actions with these preferred aspects of the world (Klin et al., 2003; Shultz et al., 2018). These same assays of social visual engagement, which demonstrate, for example, a broad sense heritability equal to about 0.90 (for summary levels of eye-looking), are pathognomonically impaired in infants later diagnosed with ASD, with differences observed from at least 2 months onwards (Jones & Klin, 2013), and reliably segregate toddlers with ASD from other toddlers (Constantino et al., 2017). Importantly, toddlers with ASD diverge from their peers in their moment-by-moment social attention: when viewing complex videos of social situations, typically developing toddlers will collectively focus on “hot spots of socialization,” or locations on-screen at specific moments in time, which carry most of the information they need to process in order to understand and successfully adapt to the social scene. In measuring these moment-by-moment patterns of social visual engagement (Constantino et al., 2017), toddlers with ASD diverge from their peers hundreds of times over a period of no more than 5–6 min of video watching. These divergences represent missed opportunities for social learning. If transposed into their real-life social experiences, these results would indicate that toddlers with ASD may miss thousands of opportunities for social learning every day, and several million opportunities for social learning within their first 2–3 years of life. This is the magnitude of the accrual of atypical experiences over time resulting from recurrent moment-by-moment deviations. These divergences not only sculpt a child's experiences over time; they also sculpt abnormal brain structures and connections as evolving physical instantiations of atypical development.

#### *On “dyadic social neuroscience”*

The study of social development over the past several decades has revealed that the relevant unit of scientific focus is the infant–caregiver dyad, and the iterative context associated with mutually reinforcing and adapted social and communicative *inter*-action (Klin, 1989; Shonkoff & Bales, 2011; Shultz et al., 2018). Innate predispositions to orient to social stimuli serve as strong engaging signals to caregivers, who at once constrain the world around the child and strengthen the infant–caregiver context (by their reciprocal engagement); upon this foundation, ever increasing and more complex cycles of contingency evolve, from birth over the course of the first two years of life. The emphasis on the dyad, rather than on child or caregiver separately, provides the most important context in which to consider Gene  $\times$  Environment interactions, as the caregiver is the most present, stable, and contingently active aspect of the baby's environment. While an infant's social visual engagement with the surrounding environment is under strict genetic control, the product of this exploration is not chained to this genetic determinism because the caregiver, though exquisitely attuned to the baby, is nevertheless free to influence and guide the interaction, to create a baby's experience as one of the “dancers” in this mutually reinforcing choreography. The most important lesson here is that the baby's biology of adaptation cannot be viewed separately from its environment, particularly from its social environment (i.e., the caregiver), which is, as noted, subject to stochastic (or chance) events, intrinsic predispositions (e.g., caregiving style), and/or external manipulations (e.g., in the case of caregiver coaching).

#### *On heterogeneity and homogeneity*

As noted, ASD is one of the most highly heritable of all complex neuropsychiatric conditions (Constantino et al., 2013) but no single molecular marker defines its diagnosis. Instead, current estimates suggest that hundreds of genetic and genomic disorders (Betancur, 2011)—the majority of which are still unknown—may play a role in etiology, including rare and common variants (Geschwind & State, 2015; Sanders et al., 2015). No single gene has yet been associated with more than a fraction of patient cases, in fact less than 1% (Chaste et al., 2015), and the extent to which any pattern of gene variants or expression can reliably indicate risk of the condition remains unclear. There are numerous hoped-for future insights into the developmental neurobiology of ASD (State & Sestan, 2012), but the condition is still diagnosed behaviorally by the presence of its defining characteristics, via direct behavioral examination and historical information (Volkmar, Lord, Bailey, Schultz, & Klin, 2004). There is, however, vast phenotypic heterogeneity, spanning the entire range of IQ and language function, with variable profiles of strengths and deficits, symptom characteristics, change over time, and comorbidities with common psychiatric conditions such as anxiety, mood, and attentional disorders (Tordjman et al., 2017). Adding additional layers of complexity to both genotypic and phenotypic heterogeneity is the notion that there are additional phenotypic routes to ASD, including serious pre- and neonatal medical conditions known to be associated with deleterious effects on early brain development, such as extreme prematurity (Joseph et al., 2017a) and congenital heart disease (Razzaghi, Oster, & Reefhuis, 2015), both of which represent a manifold higher risk increase for ASD.

Given the multiplicity of possible causes, and the phenotypic expression of so many “autisms” (Insel, 2010), a timely question might be “from where does the homogeneity of ASD arise?” In

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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 (Karmiloff-Smith, 1998; Oyama, 2000). One possibility is that 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. Or, in other words, the homogeneity of ASD may come not from some common final pathway among hundreds of initial causes but from commonalities on what these causes disrupt, namely infant-caregiver reciprocal social interaction (Jones & Klin, 2009). As noted, early brain development happens in the context of a baby's use of mechanisms of adaptive action, mechanisms that are present at birth or shortly thereafter. 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, therefore, that typically developing infants show a number of highly conserved skills that facilitate engagement with others. In contrast, infants and toddlers with ASD display early disruptions in these foundational skills, which represent early departures from normative processes. Following from the experience-expectant model of child development (Greenough, Black, & Wallace, 1987; Johnson & Karmiloff-Smith, 2004), in which the genetically determined schedule of neural 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 (Bates, Benigni, Camaioni, Bretherton, & Volterra, 1979). 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 ASD (Klin et al., 2003).

This account of heterogeneity in typical and atypical individual differences was probably put forward most succinctly by Charles Nelson: "... because so many aspects of development are activity-dependent, we should not be surprised to observe a broad range of individual differences; after all, given differences in prenatal histories, in genomes, in rearing environments, in caretaking, and in inculturation, to name just a few, each brain is left to incorporate experience differently. This, in turn, will result in differences in how infants embrace their environments, which in turn will lead to further differences in neural substrate ... *ad infinitum*" (Nelson, 1999, p. 425).

## Summarizing Features of an Early Brain Development Re-definition of ASD

The previous discussion would necessitate a distinction between the genetic risk that children are born with from the disorder that emerges in the second and third year of life. To make this distinction clear, we use here the term "autism" to signify the genetic risk, and the term "ASD" to signify the disability that may result from the genetic risk a child is born with. As such, one might tentatively define ASD according to the following criteria.

- ASD is a common neurodevelopmental disability emerging in the second year of life, typically but not exclusively of complex genetic origins, that results from early disruptions of foundational mechanisms of socialization.
- ASD is marked by heterogeneous expressions of social, communication, sensory, and behavioral disabilities and rigidities, which may be associated with significant intellectual and language impairment.
- "Autism" is a common inborn risk, highly heritable and genetically complex, representing the extreme expression of a normally distributed trait or constellation of traits in the areas of social and communicative function.
- Autism places a child at risk for ASD via the effects of early, frequent and cumulative disruptions of reciprocal social interaction, caused by the child's attenuated engagement with others and inability to adaptively adjust to the demands of the surrounding social environment.
- In the first year of life, evidence that autism is leading to ASD comes from measurements of deviation from social and communicative milestones, which are reduced, particularly in regards to social visual and social vocal contingent interactions with others.
- In the second year of life, evidence that autism is leading to ASD comes from observations of ASD symptoms, which become more pronounced toward the second half of the second year of life.
- Because autism as a profile or constellation of traits is instantiated in dynamic social environment, its expression is influenced by the caregiving behavior of others as well as by other environmental factors and chance events, particularly insofar as they impact the social context of child-caregiver relationship and experiences.

## Implications of an Early Brain Development Re-definition of ASD for the Early Detection and Intervention Enterprise

By building a re-definition of ASD for vulnerable infants and toddlers on the basis of principles and science of typical early brain development and disruptions thereof seen in the early pathogenesis of ASD, it is possible to draw a number of conclusions that have direct impact on challenges and opportunities associated with research and policy of early detection and treatment in ASD.

- Waiting to begin treatment for their social communication and behavior vulnerabilities until a diagnosis of ASD is attained means missing the period of a child's greatest neuroplasticity, the most favorable window of opportunity to optimize outcomes and attenuate symptoms.
- More accurate and quantitative early detection of risk for ASD, including prodromal and very early expressions of the condition, are becoming possible through measurements of

- early-emerging social and communicative behavior, and, specifically, deviations from normative skills (not unlike a child's falling percentile on a growth chart for physical height or weight).
- The more we wait to intervene in order to course-correct an atypical developmental path, like in ASD, the more entrenched it becomes, and the more difficult it is to change it.
  - Given the cascading nature of child development (the canalization principle), minor deviations from normative development early on can accrue with time and become not only major deviations but actual aberrant behaviors, or symptoms, which then beget more symptoms via associative learning (e.g., Moriuchi, Klin, & Jones, 2017).
  - The converse is also true: were we to be able to normalize early learning experiences to some extent, this could have an outside effect downstream in development because this would not only alleviate severity of symptoms but would also create its own cascade toward more typical experiences and the acquisition of normative skills resulting from these experiences.
  - A child's development is the product of mutually reinforcing adaptive action between child and caregiver. Whereas a child's attenuated draw to others, like in the case of ASD, will impact the product of social interaction thus limiting the learning experience, a caregiver's deliberate compensation may potentially attenuate the disruption and normalize somewhat the social-communicative interaction, and, in this way, promote the child's learning. For example, parent coaching has been shown to significantly increase conversation turns and advance infant language development (Ferjan Ramírez, Lytle, & Kuhl, 2020).
  - Most evidence-based early treatment modalities in ASD are caregiver-mediated. We might not be able to engineer a child "better genes," but we might be able to engineer the kind of environment surrounding the child that would promote, probabilistically, less deviant behavior and more normative behavior. The most important component of the surrounding environment is, of course, the child's caregiver, and the engineering of caregiver behavior is indeed the main principle underlying current evidence-based early treatments for ASD (Dawson et al., 2010; Ingersoll & Wainer, 2013).
  - Engaging caregivers as allies in the treatment of children does not mean an intervention meant to "correct bad parenting" or to somehow correct something that parents are not doing right. The causative disruption of the child-caregiver unit of development is the instantiation of the child's genetic risk. For most children, the redundancies and robustness of social-communicative predispositions and contingencies of the child-caregiver relationship, "good enough" caregiving is sufficient to move social-communicative development forward. But in the case of vulnerable infants and toddlers, there is a need to train and support caregivers, to deliberately engineer social interactive engagement using behavioral principles (Schreibman et al., 2015), so that caregivers can leverage every moment of daily experiences to promote social-communicative development (Wetherby et al., 2014), thus alleviating the deleterious implications of thousands of missed opportunities for social learning experienced by infants and toddlers with ASD every day.
  - In contrast to ethical concerns debated in the past (Yudell, Tabor, Dawson, Rossi, & Newschaffer, 2013), parents of babies at high risk for ASD are reassured and feel supported by, and thankful for, prospective monitoring and expert guidance. There is some evidence to suggest that this form of cost-effective and community-viable practice is in itself beneficial for children's outcomes (Micheletti et al., 2020), and parent-coaching practices may have benefits for a much broader range of vulnerable children including those growing up in low-income environments (Ferjan Ramírez et al., 2020) (see below), thus allaying fears of the cost of "false positives" in universal screening, which tend to be children with non-ASD developmental concerns that are actionable and likely to benefit from early intervention (e.g., Robins et al., 2014).
  - Given the multiplicity of causes of ASD, the homogeneity of phenotypic expression (the fact that despite vast behavioral heterogeneity there is great validity in the nosologic category), comes from what the various causes disrupt (rather than commonalities across the causes), namely reciprocal social interaction between child and caregiver, which is the universal platform for early social and communicative brain development. In this light, ASD as a clinical construct stands for social communication very much like intellectual disabilities as a clinical construct stands for cognition. It is no surprise that ASD is almost as common as intellectual disabilities. And it should follow that, like intellectual disabilities, where the cognitive trait is measured in terms of deviation from norms, in ASD the social communication trait should be measured in terms of deviation from norms.
  - That ASD may represent the result of disruptions of reciprocal interaction (which acts like a final common pathway among myriad etiologies) is supported by the multifold increase in risk for ASD in children born with medical conditions known to impact early brain development, specifically white matter injuries, such as extreme prematurity (Hinojosa-Rodríguez et al., 2017) and congenital heart disease (Licht et al., 2009; Wernovsky & Licht, 2016). Interestingly, brain development abnormalities in both conditions have been deemed to be similar, but the question is whether an ASD phenotype in these two populations is associated with brain injuries of specific significance to early social development (Shultz et al., 2018). The entrenched view that ASD can only be of a syndromic or "sporadic" genetic form, and it cannot result from some other etiology capable of disrupting social behavior and brain, is often apparent when scientists at times comment that say the 8% (Joseph et al., 2017b) or so of infants born extremely preterm who end up with an ASD diagnosis have a "different kind" of ASD, and that neurodevelopmental research of these infants cannot help elucidate ASD pathogenesis. And yet, the "ASD" found in these populations does not appear to be, phenomenologically and clinically, different from the more traditional genetic kind, as indicated in practice parameters for these conditions (e.g., Marino et al., 2012).
  - As noted, other cohorts of vulnerable children may present with opportunities for treatments intended to support early social and communication development, including those with other neurogenetic etiologies such as children with Fragile X and Williams syndrome, or children born in adverse conditions such as poverty: in all of these cases, there is a higher than expected prevalence of autism-related social and communication disabilities (Boat & Wu, 2015; Crespi & Procyshyn, 2017; McCary & Roberts, 2013).
  - Because the unit for research of behavior-brain social and communicative development is the child-caregiver relationship, experience, and environment, there should be rigorous quantification of environmental features influencing this unit (Berman et al., 2019), particularly sociodemographic variables (Bornstein et al., 2013) and adverse childhood experiences

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### Caveats

To energize a research enterprise aimed at probing the possibilities for optimized outcomes afforded by a developmental psychopathology view of ASD does not mean that the state of the science is such that we already know that treatments and interventions building from this view are going to be successful, nor that we know exactly what are the most effective active ingredients. In fact, there are cautionary tales suggesting otherwise (e.g., Whitehouse, Varcin, Alvares, Barbaro, & Hudry, 2019), which point to the need for early treatment research that will probe, in larger samples and with much greater specificity and definition of active ingredients, the efficacy of caregiver-mediated treatments (Kasari, 2019). Given the promise of gains with lifetime implications, it is disappointing that this literature has been slow to grow. And yet, progress has been made, and evidence for the beneficial effects of caregiver-mediated treatments is accruing in regards to children with ASD and developmental delays (e.g., Kaiser & Roberts, 2013; Roberts & Kaiser, 2015; Stern, Maltman, & Roberts, 2017) and with other inborn vulnerabilities (Roberts, 2019).

It is nevertheless important to emphasize that caregiver-mediated treatments are not simply a convenient treatment modality, chosen because of its being less expensive and more community-viable than expert-delivered treatments, and more readily funded via IDEA Part C. The case for caregiver-mediated treatment, as noted, builds on some 20 years of research on the criticality of infant-caregiver dyadic contingency as an evolutionarily-conserved, early-emerging, platform for social communication development from birth on (Feldman, 2007, 2017). These synchronies are quantified from the first weeks and months of life (e.g., Jaffe, Beebe, Feldstein, Crown, & Jasnow, 2001) and remain operational throughout one's life via subliminal, synchronized behavioral communicative signals (e.g., Hömke, Holler, & Levinson, 2018), and at the neural level (Kinreich, Djalovski, Kraus, Louzoun, & Feldman, 2017).

Having said that, one important lesson from attempts to engineer the environment of vulnerable children in order to effect beneficial change is that our knowledge of environmental factors, and particularly, our ability to quantify their effects, are still limited. This is evident not only in ASD research and, in fact, more illustrative cautionary tales originate from other fields. For example, a recent large study showed that concordance rate of schizophrenia in identical twins is a surprisingly low 33%, suggesting untapped opportunities to prevent this serious mental health condition using knowledge of nonshared environment, or chance, influences (Hilker et al., 2018). In other words, after decades of research of schizophrenia, our knowledge of pre-emptive interventions is still limited. This situation is even more striking in ASD research. In a recent study focused on monozygotic twin concordance and discordance for autistic trait severity, while probandwise concordance for ASD was an extremely high .96, the concordance rate for variation-in-severity of symptomatology had an  $R^2$  on the order of .1, indicating that profile and level of disability in identical twins with ASD is substantially influenced by nonshared environmental factors; this is an intriguing finding raising the possibility for novel targets of early ASD amelioration but as yet unknown (Castelbaum, Sylvester, Zhang, Yu, & Constantino, 2019).

Despite these disappointments, advances are being made, and this is particularly evident in the emerging field of "Environmental Neuroscience" (Berman et al., 2019), which builds from developmental systems theory (Oyama, Griffiths, & Gray, 2001) to chart and quantify the unfolding interactions occurring across brain-behavior and physical-social environments. The focus here is on "emerging phenomena" (Anderson, 2015), which is what ASD has been hypothesized to be (Shultz et al., 2018), within this multiscale science promoting the study of cycles of contingency occurring within and across this gene-brain-behavior-environment framework of analysis (Nelson, 1999).

### Concluding Thoughts

To re-define ASD in early brain development terms is to revisit the world of opportunities afforded by current science to optimize children's outcomes despite the liabilities that they are born with. It is to counter outdated notions that devastating disability is determined the moment a child is born, and that these burdens are inevitable, with only improvements being some alleviation of symptoms and increased independent-living skills. The impetus for writing this opinion piece is the concern that such views of neurodevelopmental conditions such as ASD can become self-fulfilling science and policy in ways that are diametrically opposed to what we currently know, and are learning more every day, of how genetic liabilities become, or not, instantiated as lifetime disabilities.

This approach is difficult to contemplate when one's experience of ASD is of a child, adolescent, or adult whose clinical presentation is marked by self-injury, aggression, thrashing behavior, and life-threatening elopement. But this approach is now difficult to avoid if one accompanies babies' first year of life on a path to ASD. These two contexts generate two levels of scientific and policy discourse. Unless they are reconciled by the emerging science of gene-brain-behavior interdependencies in the neuroscience of early brain development, there is concern that the world of opportunities made possible by early detection and early treatment will remain under-powered.

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**Conflicts of Interest.** This conceptual piece did not include original empirical work, but it covered themes associated with early diagnosis and intervention for young children at risk for ASD. In this light, Drs. Jones and Klin, among the co-authors of this manuscript, wish to disclose that they are equity holders in, and inventors of the technologies deployed by, EarliTec Diagnostics. EarliTec is a company that develops medical devices for early diagnosis of ASD and gives a portion of its revenue to support treatment of children with ASD.

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