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The emergence of autism spectrum disorder: insights gained from studies of brain and behaviour in high-risk infants

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Purpose of review
We review studies of infants at risk for autism spectrum disorder (ASD), proposing that the earliest manifestations of disrupted brain development can shed light on prebehavioural markers of risk and mechanisms underlying the heterogeneity of ASD.

Recent findings
Prospective, longitudinal studies of infants at risk for ASD have revealed that behavioural signs of ASD are generally not observed until the second year of life. The developmental signs within the first year are often subtle and rooted in processes outside the core diagnostic domains of ASD, such as motor and visual perceptual function. However, studies examining early brain development and function have identified a myriad of atypicalities within the first year that are associated with risk for ASD.

Summary
Longitudinal studies of high-risk infants provide a unique opportunity to identify and quantify the sources of the atypical development and developmental heterogeneity of ASD. Integration of assays of behaviour and brain in the first year of life, expansion of the definition of high risk, and coordinated efforts in multisite investigations to adequately power integrative studies will lead to new insights into mechanisms of atypical development and, ultimately, the ideal timing and target for interventions that aim to attenuate delays or impairments.

Keywords
autism spectrum disorder, behaviour, cognitive neuroscience, early development, neurodevelopment

INTRODUCTION

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by impairments in social communication skills and the presence of restricted interests and repetitive behaviours [1]. ASD is truly a spectrum of conditions, with considerable variability across individuals in cognitive function, language ability, and psychiatric and neurological comorbidities. This heterogeneity poses a tremendous challenge to the development of more tailored approaches to diagnosis, clinical monitoring, biomarker development, and treatment. In this review, we propose that studies of the earliest manifestations of disrupted brain development in infants at risk for ASD can shed light on prebehavioural markers of risk and mechanisms underlying the heterogeneity of ASD, both of which should ultimately inform timing of interventions. We provide an overview of studies of high-risk infants, emphasizing the fact that overt behavioural

measures may fail to identify the earliest features of neurodevelopmental disorders but that studies of brain function, through electroencephalography (EEG), MRI, and eye tracking, have identified differences in the first year of life. We then discuss key future directions in these longitudinal studies.

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KEY POINTS

- Prospective, longitudinal studies of infant siblings of children with ASD have revealed that behavioural signs of the disorder do not emerge until the second year of life.

- Behavioural signs of atypical development within the first year of life are limited and of those that have been identified, appear to be subtle, more sensitive to risk status than ASD outcome, and lie outside of core ASD diagnostic domains.

- Studies using developmental neuroscientific techniques to examine early brain development have unveiled a myriad of differences in brain structure and function within the first year of life in infants who later meet criteria for ASD.

- Studies of very early brain development in infants at risk for ASD have the potential to shed light on the prebehavioural markers of risk and mechanisms underlying the heterogeneity in ASD.

- Future brain-based research will benefit from larger samples to delineate meaningful subgroups and examine brain–behaviour correlations, examination of predictive markers across more continuous developmental domains, and the inclusion of other at-risk populations alongside infants at high familial risk.

THE PROBLEM OF HETEROGENEITY

It has been proposed that the clinical heterogeneity in ASD results, in part, from the etiologic heterogeneity of the syndrome. In addition to environmental and medical risk factors, such as prenatal drug exposure, preterm birth, or congenital infection, hundreds of genetic variants have been identified that contribute to the development of ASD. In fact, up to one-third of individuals with ASD have an identified, causative genetic variation [2]. Although these variations impact specific molecular pathways that can lead to distinct clinical presentations, the various functions of many of these genetic variants converge in the regulation of fundamental processes of early brain development such as cortical organization, synapse structure and function, connectivity, and the excitation/inhibition balance [3,4■]. As we elucidate these genetic mechanisms, key questions emerge. How early do these convergent processes diverge into distinct developmental pathways, and can they be captured through tools in developmental neuroscience? Can we begin to identify and quantify the sources of the developmental heterogeneity of not only ASD, but of the broader spectrum of neurodevelopmental disorders, even before a diagnosis is made?

EARLY MARKERS OF AUTISM SPECTRUM DISORDER: WHAT HAVE WE LEARNED FROM STUDIES OF BEHAVIOUR?

Infants at high familial risk for ASD, based on having at least one sibling with ASD, ('infant siblings') have constituted the primary focus of research in early developmental markers of ASD, not only because they are at heightened risk for ASD, with prevalence estimates up to 20%, but also because they are identified prenatally and can be followed from birth [5–9]. These prospective, longitudinal studies of infants at familial risk for ASD have significantly advanced our understanding of the developmental progression and unfolding of ASD over the earliest years of life. A number of recent reviews have summarized current knowledge regarding early risk markers and developmental precursors to ASD in infancy and toddlerhood in high-risk infant siblings [10,11,12■■,13]. Based on this collective body of work, we now have an understanding that overt, behavioural signs of ASD do not typically manifest until the second year of life (i.e. between 12 and 24 months). Over this early developmental period, there are a number of behavioural markers that distinguish high-risk infants who go on to meet criteria for ASD, including delays or atypicalities in the use of gesture [8,14–16], eye contact [14], social attention [6,17], response to name [18], imitation [9,19,20], receptive and expressive language [5,9], and the presence of repetitive behaviours [21,22]. At 18 months of age, different combinations of these risk markers have been found to be predictive of various subtypes of ASD at 3 years [23]. Diagnoses of ASD over this second year of life (i.e. at 18 and 24 months), based on behavioural markers, have been shown to be highly stable over time [24■].

Few behavioural markers of ASD have been identified within the first year of life [10,12■■], with several hypotheses proposed for this phenomenon. Is it possible that ASD results from a typical developmental trajectory that is subsequently derailed over later infancy and toddlerhood [6]? Given our understanding of the underlying neurobiology of ASD, it is more likely that atypical behaviours in the first year are subtle, perhaps transient, and lie outside of the core domains of ASD, such as in sensorimotor development or atypical visual attention [25,26,27■■]. However, these core developmental constructs appear to be more sensitive to risk status (i.e. high risk versus low risk) rather than ASD outcome. In other words, although there are signs of atypical development within the first year in infants at risk, it is not until the second year of life that behaviours emerge that show phenotypic

continuity with and specificity for an ASD diagnosis [28]. It is also possible that the lack of behavioural signs in the first year reflects the limitations of the measures themselves, with developmental assays being constrained by the restricted repertoire of infants. Indeed, as will be discussed in the subsequent sections of this review, studies in developmental neuroscience are increasingly identifying differences in brain function and structure, as well as gaze patterns, that manifest within the first year of life and are predictive of later ASD (at least at the group level). These early markers are consistent with genetic findings implicating the prenatal and early postnatal period in ASD etiology [3].

DEVELOPMENTAL NEUROSCIENCE METHODS TO STUDY EARLY BRAIN DEVELOPMENT

The first years of life are marked by rapid and significant changes in brain development. The pace and significance of this development are not immediately represented at the level of overt behaviour (i.e. changes in the brain appear to precede changes in behaviour). Developmental neuroscience methods offer a window into this very early period of development where the ability to stratify infants on the basis of overt behaviour is limited.

MRI/diffusion tensor imaging/functional MRI

There are a number of noninvasive tools in developmental neuroscience that allow us to study different aspects of infant brain development, all with unique strengths and limitations. MRI and diffusion tensor imaging (DTI) techniques allow for the visualization of the developing anatomy and structural connectivity of the brain. Functional MRI (fMRI) provides a means in which to investigate functional networks (as opposed to structural networks) or changes in cortical activity with a degree of spatial accuracy that is unable to be obtained by other noninvasive methods. Although these methods provide invaluable information about early brain development, there are challenges in their application to infants and in their more widespread use as screening or diagnostic tools, most notably their sensitivity to motion artifact and their cost. To minimize head movement, infant studies typically require conditions of natural sleep, thus limiting the types of paradigms that can be used to study functional aspects of infant brain development.

Functional near-infrared spectroscopy

Functional near-infrared spectroscopy (fNIRS) is a relatively new technology in its application to infancy. However, over recent years, it has been increasingly applied to the study of typical and atypical brain development [29]. Similar to fMRI, fNIRS provides an indirect measure of neural activity based on haemodynamic responses in the brain, albeit with considerably lower spatial resolution than fMRI can afford. A major of advantage of fNIRS in the study of infant development is its higher degree of motion tolerance relative to fMRI. fNIRS can be used to index regional neural activity in awake infants on the cortical surface (within 2–3 cm of the scalp), allowing for the probing of a broader range of paradigms and developmental functions, including social cognitive functions [29,30].

Electroencephalography

EEG, both resting state and event related, measures postsynaptic pyramidal cell activity on a temporal scale that is close to real time. These techniques can resolve neurophysiological activity with millisecond temporal resolution, permitting the measurement of brain oscillatory patterns and dynamics at the large-scale network level [31]. Despite advances in methods around source localization, compared with fMRI and fNIRS, the spatial resolution of EEG remains relatively poor. Like fNIRS, EEG can be recorded in the awake, behaving infant, permitting the assessment of a wide range of developmental functions and neural pathways, from basic sensory processing to higher-level cognitive and social processes. EEG is relatively inexpensive compared with other imaging methodologies. Similar to MRI, EEG holds high translational potential from the laboratory to the clinic and also holds high translational potential from animal models to humans, as similar neurophysiological signals and even event-related paradigms can be applied across species [32,33■,34].

Eye tracking

Although not a measure of brain anatomy or function, eye tracking is also considered an integral tool for developmental cognitive neuroscientists, and it is commonly used in the study of early development. Eye-tracking technology provides a quantitative, objective measure of infant gaze patterns from the earliest months of life. As visual fixation and visual orienting appear to be supported by brain-wide cortical and subcortical networks in infancy [35,36], gaze patterns may represent a readout of broader cortical development and functioning. In other words, eye-tracking technology provides a bridge between analyses at the level of the brain and overt behaviour.

EARLY MARKERS OF AUTISM SPECTRUM DISORDER: WHAT HAVE WE LEARNED FROM STUDIES OF THE BRAIN?

The application of developmental neuroscience tools to the study of early development in infants at risk for ASD has revealed a myriad subtle and dynamic differences in brain function, structure, and gaze patterns over the earliest years of life (including within the first year) in infants who go on to meet diagnostic criteria for ASD.

Studies of brain structure

Imaging studies using MRI, DTI, and fMRI have identified atypical, age-dependent patterns of structural growth and connectivity early in life in infants who are later diagnosed with ASD. Emerging findings from DTI studies in particular suggest that there are age-dependent atypicalities in the microstructural organization of white matter tracts in infants who later meet criteria for ASD [37]. Specifically, Wolff *et al.* [38] identified higher fractional anisotropy at 6 months of age in high-risk infant siblings with later emerging ASD compared with infants without ASD; this increased in fractional anisotropy was followed by a slower rate of development in ASD infants such that by 24 months, ASD infants had lower values than infants without ASD. A similar pattern of high fractional anisotropy at earlier ages followed by a slower than normal rate of development in ASD infants has since been observed in community-sampled high-risk infants aged between 1 and 4 years [39▪]. MRI studies have also identified differences in various brain morphological features as early as 6 months of age in at-risk infants who develop ASD compared with infants who do not develop ASD. These features include increased extra-axial fluid [40] and increased thickness in the corpus callosum [41]. These early atypical morphological features have been linked to later ASD symptom severity [40] and restricted and repetitive behaviours [41].

Studies of brain function

In addition to early differences in brain anatomy and structure, there is evidence emerging from fMRI and EEG findings for concomitant differences in brain function early in life in at-risk infants, prior to the emergence of overt behavioural signs of ASD. Between 6 and 12 months, high-risk infants who later meet criteria for ASD show atypicalities in event-related EEG responses (defined as an event-related potential) [42,43▪] and patterns of hemispheric specialization (based on event-related

coherence analyses) [44] to facial stimuli compared with infants who do not develop ASD. Over the second year of life (at 14 months), elevated α connectivity (particularly over the frontal region) has been demonstrated in at-risk infants who later meet criteria for ASD while viewing social and nonsocial videos [45]. Alongside these differences in neural processing of social perceptual stimuli, there is also evidence from functional imaging studies of atypical auditory processing. fMRI studies have demonstrated atypical response patterns to human voices in infants at high risk for ASD between 4 and 7 months [46▪]. Lombardo *et al.* [47] also found that activation patterns to speech sounds prior to receiving an ASD diagnosis was associated with later language outcomes among children with ASD, highlighting the potential predictive power of these methods. Although fNIRS also provides a measure of early brain function, to date, no studies have used this method to examine or predict ASD outcomes early in development. However, in studies using this technology to examine differences based on familial risk status, patterns of functional connectivity and haemodynamic responses to social stimuli (e.g. faces) have been found to differentiate infants at high risk for ASD compared with infants at low risk over the first year and as early as 3 months [48–50].

Studies have also shown differences in developmental trajectories of gaze patterns over time, as well as at fixed ages, over the first year in infants who go on to meet criteria for ASD. For example, infant siblings who later met criteria for ASD showed a decline in their attention to eyes from 2 to 6 months of postnatal life [51]. At 6 months, infants with ASD attended less to social scenes [52] and between 6 and 9 months, demonstrated shorter durations between saccades (i.e. shorter fixation durations) [53]. At 9months, infants who met later criteria for ASD showed enhanced visual search performance compared with high-risk infants without ASD [54▪▪]. Similarly, enhanced perceptual abilities at 9 months were associated with ASD symptom severity at 15 and 24 months in one study [55]. Together, these findings indicate that eye-tracking technology can reveal variations in gaze patterns within the first year of life that appear to represent predictive markers of ASD, prior to the onset of overt, behavioural signs of the disorder.

These studies of brain function and structure support the contention that changes in the brain precede changes in behaviour. There are a wide array of differences spanning alterations in morphology, structural, and functional connectivity, and responses to sensory stimuli suggestive of widespread, rather than localized, atypicalities in brain development that precede the emergence of ASD

[12""]. Moreover, in many studies, particular patterns of atypical development change across development, suggesting that the utility of any potential brain-based marker of ASD will be age dependent. Thus far, in part because of sample size limitations, the majority of studies in this area have focused only on group-level differences, thus limiting our capacity to identify meaningful subgroups (or individual differences) that may inform our understanding of convergent and divergent brain-based mechanisms in ASD.

NEXT STEPS AND FUTURE DIRECTIONS

The data reviewed here support the fact that atypical brain development and function, particularly in baseline neural connectivity as well as low-level processes (such as visual and auditory processing), gaze patterns, and social attention, can be identified in the first year of life in infants at heightened risk for ASD. These findings, largely propelled by the innovative use of technologies that provide greater precision than behavioural assays to capture neurodevelopmental processes have supported the need for more comprehensive and integrative (multimodal and multisite) studies of risk in early infancy. Studies continue to be encumbered by small sample sizes and the cost (both financial and in experienced personnel) of testing infants with these methods, thus restricting replication studies and large-scale collaborations. From a scientific perspective, several key future directions emerge from this body of work. First, because of heterogeneity in risk groups and small sample sizes, most studies to date have focused on group-level differences, either based on risk groups or diagnostic outcome. Larger samples will facilitate more sophisticated analyses of correlation between core behavioural and neuroimaging measures which, in turn, will elucidate the developmental relationship between neural networks and function and atypical behaviours. In fact, several infant consortia have been developed to achieve these goals, including the international Baby Sibs Research Consortium (BSRC) as well as the Infant Brain Imaging Study (IBIS).

Second, much of the focus of these early measures has centred on prediction of ASD. However, it is well appreciated that at least one-third of infants at high familial risk for ASD exhibit delays or atypical features outside of the autism spectrum, such as motor delays, language impairment, intellectual disability, or attention deficit hyeractivity disorder [56"]. Studies need to examine the specificity and sensitivity of these brain markers to ASD alongside predictive markers across more continuous developmental domains, such as motor function, sensory processing, social attention, and even behaviour regulation to inform our understanding of the biological underpinnings and precursors of a broader range of neuropsychiatric conditions.

Finally, future studies must also expand upon the definition of risk, leveraging changes in practices around genetic testing. Other risk groups have emerged with earlier, targeted genetic testing in infants. In a recent meta-analysis of ASD phenomenology across genetic syndromes [57"], reported rates of ASD ranged from 10 to 60%, depending on the specific genetic cause. These authors and others have argued for the need for research comparing ASD profiles between syndromes and between syndromic and nonsyndromic forms of ASD, as these efforts can shed light upon convergent and distinct mechanisms of atypical development [58"]. Most comparison studies of this type have been performed cross-sectionally, well after an ASD diagnosis is made and often after neurological comorbidities, such as epilepsy, have emerged that may obscure the core behavioural manifestations of ASD [59,60]. Relatively unexplored remain the earliest behavioural and biological markers of risk in these infants, the unfolding of ASD in very early infancy (especially in the 0–6 month postnatal period), and the comparison of these developmental processes in defined genetic syndromes with familial risk groups. Of course, part of the challenge lies in the reduced sample sizes in rare disorders and the delayed timing of genetic diagnoses in conditions where clinical manifestations prompting the genetic diagnosis do not emerge until later in childhood. However, in disorders where prenatal diagnosis occurs more readily, including monogenic syndromes such as tuberous sclerosis complex and copy number variants such as 22q11.2 deletion syndrome, prospective studies are not only feasible but necessary.

Finally, these prospective, natural history studies of risk must be coupled with studies of early intervention, with strategies for modulation timed to the earliest expression of atypical development. These integrative studies can focus not on prediction of outcome but on defining the earliest markers of risk, determining their sensitivity to ASD versus other neurodevelopmental disabilities, and then identifying the exact targets for intervention with outcomes defined by changes in both brain and behaviour.

CONCLUSION

The ultimate goal for translational research in neurodevelopmental disorders lies in the optimization

of clinical outcomes through the most effective, targeted, and timely treatments. This goal becomes hampered by the tremendous etiological, biological, and clinical heterogeneity of disorders such as ASD, particularly as we attempt to examine brain–behaviour relationships in childhood and adulthood. Studies of early infancy, rooted in a fundamental hypothesis that disruptions in brain development precede the emergence of clinical symptoms, hold tremendous promise in improving our understanding of the timing and type of disruptions that can be modulated with both pharmacological and behavioural interventions.

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Conflicts of interest

S.S.J. serves as a consultant for Roche pharmaceuticals. The remaining author declares no conflict of interest.

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