Prediction of autism in infants: Recent progress and future challenges

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Abstract

Autism is a neurodevelopmental condition that can be reliably diagnosed in children by the age of 18-24 months. Prospective longitudinal studies of infants ≤ one year of age who are later diagnosed with autism are elucidating the early developmental course of autism and identifying ways of predicting autism before diagnosis is possible. Studies using MRI, EEG, and near infrared spectroscopy have identified differences in brain development in infants later diagnosed with autism compared with infants without autism. Retrospective studies of medical records of infants below age 1 who received a later diagnosis of autism have also revealed an increased prevalence of health conditions, such as sleep disorders, gastrointestinal disorders, and vision problems. Behavioural features of infants later diagnosed with autism include differences in attention, vocalisations, affect, temperament, social engagement, sensory processing, and motor abilities. While research findings offer the promise of infant autism screening tools, individual-level prediction remains a future goal. Multiple scientific challenges and ethical questions remain to be addressed to translate research on early brain-based and behavioral predictors of autism into feasible and reliable screening tools for clinical practice.

Introduction

Autism spectrum disorder (autism) is a neurodevelopmental condition characterised by qualitative differences in social communication abilities and restricted interests and repetitive behaviours, which can be reliably diagnosed in children by age 18-24 months. Technological and scientific advances have led to a better understanding of patterns of brain and behavioural development in infants $\leq$ 12 months of age who are later diagnosed with autism. Research suggests that we are on a path to earlier detection of autism during infancy, a period of rapid brain development when intervention might have greater potential to influence later outcomes. However, challenges of individual-level prediction, substantial implementation barriers, and the heterogeneity of autism must be addressed before scientific research on infant prediction of autism can be fully translated into useful screening tools for clinical practice. Furthermore, most studies prospectively followed infants who have an older sibling diagnosed with autism ("infant siblings") who have been shown to have an increased likelihood of an autism diagnosis due to genetic factors.[1] In most studies, infant siblings with and without later autism are compared with infants with no family history of autism ("low likelihood infants"). While this has been a powerful approach that has provided insight into infant development in autism, the generalisability of findings from this subgroup to the broader autism population remains to be demonstrated.

In this commissioned review, we summarize recent advances and ongoing challenges in prediction of autism during infancy, with a focus on three domains: (1) brain development based on MRI, EEG, and near-infrared spectroscopy (NIRS) findings; (2) physical health; and (3) behavioural development. We first describe recent findings (primarily 2016 or later) and then discuss the challenges and questions that remain to be addressed in the future to facilitate translation of research findings into validated tools for clinical application**.**

Brain-based biomarkers for autism

In this section, we describe the most recent evidence of differences in brain development that could prognosticate autism in infants, starting with MRI studies and then neurophysiological findings (EEG and NIRS). Several longitudinal, prospective studies of potential predictive brain-based biomarkers have elucidated multiple differences in brain development that emerge at or before the onset of early behavioural precursors of

autism. Several methods have been used to describe infant brain structure and function, each of which provides a unique perspective on brain development (see panel 1). MRI findings, along with preclinical research on animal models of syndromic autism, implicate differences in neural progenitor proliferation and neurogenesis in the neurobiology of autism.[2] Alterations in the inhibitory-excitatory balance at system, neuronal, and synaptic levels might also influence the early development of brain circuitry in autism, reflected in a wide range of EEG differences in the first year of postnatal life.[3] As behavioural features emerge, differences in the ways the infant is interacting with the environment likely further shape the development of experience-dependent neural circuitry.

MRI

Recent prospective MRI studies have identified multiple differences in early brain development of infants later diagnosed with autism. To begin, brain overgrowth (size) in the first and second years of postnatal life has been demonstrated in infant siblings subsequently diagnosed with autism.[4] In comparison to infant siblings who were not diagnosed with autism, those with later autism have been found to exhibit accelerated growth in cortical surface area from 6-12 months, especially occipital, temporal, and frontal lobe regions, which has been found to precede brain overgrowth occurring between 12 and 24 months.[4] Accelerated amygdala growth has also been shown to distinguish 6-month-old and 12-month-old infant siblings subsequently diagnosed with autism from those with fragile X syndrome, infant siblings without autism, and those with neurotypical development.[5] A prospective, longitudinal study of 50 infants (24 infant siblings and 26 low likelihood infants) found enlargement of subcortical regions in 4–6-month-old infant siblings (regardless of later diagnosis).[6] A longitudinal study that compared infant siblings later diagnosed with autism (n = 86), infant siblings with early language delay (n = 41) and infants who did not receive a diagnosis of autism or language delay (n = 255 and 143, respectively) found that, by 12 months of age, enlarged subcortical structures predicted later autism versus language delay.[7] Using a prospective longitudinal design with infant siblings (n = 270) and low likelihood infants (n = 108), enlarged corpus callosum at 6 months -- but not 24 months -- predicted an autism diagnosis, suggesting a dynamic process of early development of the corpus callosum.[8]

In a study of infant siblings (n = 92), measures of fractional anisotropy (FA; a measure reflecting degree of myelination and axonal density) revealed differences in the developmental trajectory from 6-24 months of age of white matter in those infants who were later diagnosed with autism, characterised by increased FA at 6 months followed by slower change over time in FA values through 24 months.[9] A study of 116 infant siblings reported differences in white matter network efficiency in 6-month-old siblings later diagnosed with autism.[10] Variations in white matter development in distinct brain structures in infants subsequently diagnosed with autism have been correlated with specific autism-related behaviours.[2]

A longitudinal study of 221 infant siblings and 122 low likelihood infants found that increases in extra-axial CSF volumes at 6 months of age predicted later autism and were found to be stable through 24 months.[11] CSF contains growth factors that influence neuronal proliferation and has been hypothesized to play a role in clearing metabolites, including amyloid beta and pro-inflammatory cytokines, that can affect brain function.

A study of resting-state functional MRI (fMRI) during sleep found disruptions in thalamocortical connectivity and language-related networks by 1.5 months of age in infant siblings, regardless of later diagnosis.[12] Six-month-old infant siblings with atypical patterns of functional connectivity based on fMRI were more likely to be diagnosed with autism at 2 years than infant siblings without an autism diagnosis.[13]

Individual-level prediction. Most MRI studies to date have assessed potential biomarkers that discriminate groups of infants with or without a later diagnosis of autism. Only a few of these studies have provided data on individual-level prediction accuracy (table 1). An algorithm combining measures of extra-axial CSF, brain volume, age, and sex at 6 months predicted which infant siblings were later diagnosed with autism with sensitivity of 0.66 and specificity of 0.68.[11] Using machine learning , surface area growth features from 6-12 months predicted diagnostic outcomes in infant siblings with 0.88 sensitivity and 0.95 specificity.[4] Using cross-validated machine learning, whole-brain resting-state fMRI at 6 months predicted later autism in infant siblings with 0.82 sensitivity and 1.00 specificity.[13]

Electrophysiological biomarkers

Infant recordings of auditory brainstem responses (ABR), spontaneous EEG, and event-related potentials (ERP) have revealed differences in timing, amplitude, and spectral power that could serve as potential brain-based biomarkers of autism. Retrospective analysis of routinely collected ABR hearing screening data in 139,154 newborns (321 later diagnosed with autism) has revealed prolongations of the ABR phase and V-negative latency in newborns later diagnosed with autism.[14] Research using machine learning to analyse spontaneous EEG from 99 infant siblings and 89 low likelihood infants found that EEG complexity[15] and longitudinal features of multiple power spectral densities predicted autism.[16] In a study designed to replicate an earlier report that increased 7-8 Hz EEG connectivity at 14 months was associated with a diagnosis of autism,[17] this EEG biomarker was only associated with level of restricted interests/repetitive behaviours.[18] Among 8-month-olds (116 infant siblings and 27 low likelihood infants), increased cortical reactivity to repeated tones (reduced repetition suppression of 40-60 Hz evoked gamma and greater 10-20 Hz inter-trial coherence) was associated with a diagnosis of autism.[19] Six-month-old infant siblings later diagnosed with autism were found to have less robust ERPs to face stimuli and shorter epochs of visual attention to faces.[20] Six-to-ten-month-old infants subsequently diagnosed with autism showed lower theta inter-trial coherence during face processing.[21] Eight-month-old infants later diagnosed with autism exhibited a diminished face-sensitive N290 ERP component. Prediction was improved when adding autism polygenic scores to the N290 latency to face and non-face stimuli to the model as an independent variable.[22]

In clinical trials, EEG measures have also been used to assess the effects of early interventions designed to promote social engagement during parent-infant interaction. Infant siblings who received a parent-delivered social intervention showed a developmental pattern in both EEG (frontal theta power) and ERP (P400 response to faces) that was similar to neurotypical infants and differed from infants who did not receive the intervention.[23]

In a study of 8-month-old infants (91 infant siblings and 40 low likelihood infants), spatiotemporally defined microstates (duration of social attention-related microstates) predicted a diagnosis of autism.[24] In another study of 161 infant siblings and 71 low likelihood infants, linked independent components analysis was

used to extract patterns of variation across multiple measures of cognitive and adaptive functions, autism-related behaviours, and ERP responses to eye gaze shifts, to identify cross-domain patterns that were associated with a subsequent diagnosis of autism.[25]

Individual-level prediction. Studies that have examined individual-level prediction suggest that electrophysiological biomarkers show promise as a method for early screening, as evidenced by the high sensitivity and specificity values as early as the first three months of life (table 1). In a retrospective study of clinical ABR recordings taken at 0-3 months from 30 infants later diagnosed with autism and 30 case-matched controls, a pattern of prolonged ABR wave-V distinguished the two groups with .80 specificity and .70 sensitivity.[26] In a longitudinal study of both siblings and low likelihood infants, EEG power (particularly delta and gamma) trajectories from 3-12 months reliably predicted infant siblings later diagnosed with autism with 0.82 sensitivity and 0.86 specificity.[16] Furthermore, an algorithm that included nonlinear EEG features (e.g., entropy and detrended fluctuation analysis) predicted later autism versus combined low- and high-likelihood infants (siblings) as early as 3 months with sensitivity of 0.82 and specificity of 0.99.[15]

Near infrared spectroscopy

NIRS has the advantage over fMRI of being readily usable in awake infants and toddlers while they are engaged in activities, albeit with lower spatial resolution (see figure 1). Brain responses to viewing social videos were compared to those elicited by non-social images, and human vocal sounds to environmental noises, in 4–6-month-old infant siblings.[27] Infants later diagnosed with autism showed reduced activation to the social videos across inferior frontal and posterior temporal regions, and enhanced activation to environmental noises relative to vocal sounds.[28] In another NIRS study of 32 6-month-old infants (of which 14 were infant siblings), infants later diagnosed with autism had reduced brain responses to speech sounds in bilateral anterior areas.[29]

Early physical health conditions associated with autism

Autism has been reported to be associated with higher rates of co-occurring medical conditions compared with populations of individuals without an autism diagnosis, many of which are present in the first year of life prior to autism diagnosis.[30] Conditions such as epilepsy, sleep disruption, vision problems, and nutritional

deficiencies during early postnatal development can influence trajectories of early brain and behaviour development, interacting with genetic vulnerabilities, and are a potential target for early intervention.

Among the early medical factors associated with autism are sex-specific and variable differences in head circumference, preterm delivery and low birth weight, perinatal stroke/hypoxia, and presence of congenital malformations or genetic syndromes.[31,32] The odds of an autism diagnosis are estimated to be 3.3 times higher in children born preterm than in the general population.[33] Epilepsy, including infantile spasms, is more prevalent in individuals diagnosed with autism than the general population.[34,35] In a prospective study of 432 6–12-month-old infants (71 infant siblings later diagnosed with autism, 234 infant siblings without autism, and 127 low likelihood infants) infants diagnosed with autism had higher rates of parent-reported sleep onset problems, which were correlated with differences in hippocampal volume trajectories.[36]

Studies using EHR to examine physical health profiles of children diagnosed with autism have substantiated the high prevalence of medical conditions during infancy. A study of medical records found that, during the first year of life, infants later diagnosed with autism were over threefold more likely to visit an ophthalmologist, gastroenterologist, or neurologist than those without a subsequent autism diagnosis.[30] Infants later diagnosed with autism were also more likely to have nausea/vomiting and abdominal pain.[30] Another study based on medical records (3911 autism cases and 38,609 controls) found that in the first three years of life, higher rates of neurological, nutrition-related, genetic, ear, nose and throat, and sleep conditions were associated with a higher likelihood of a subsequent autism diagnosis.[37] Significantly, infants later diagnosed with autism versus other neurodevelopmental conditions, such as attention-deficit/hyperactivity disorder (ADHD), show distinct patterns of early medical conditions.[30]

Leveraging large electronic health record (EHR) data sets, autism prediction models are beginning to be developed based on machine learning of health care data collected during routine visits during infancy.[30] For example, EHR data were used to cluster children based on their medical conditions prior to an autism diagnosis and demonstrated prediction of an autism diagnosis.[37]A recent study used machine learning based on early medical conditions to predict later autism status with encouraging results.[38]

Early behavioural markers of autism

In this section we further describe a wide range of behavioural markers of autism that are observed in infants ≤ 12 months of age. These include differences in patterns of attention, prelinguistic development, affect, temperament, social engagement, sensory sensitivity and habituation, motor abilities, toy play, and restrictive/repetitive behaviours.

Attention

Attention differences are characteristic of autism and underpin the infant's ability to select and process specific features in their environment to the exclusion of others. These differences vary depending on the context and level of complexity (e.g., orienting versus joint attention). Early attention processes can channel subsequent development, potentially allowing for neural specialisation in specific domains. Early reduced attention to social stimuli, such as faces, voices, and gestures, has been hypothesised to have downstream effects on social development, consistent with diagnosed toddlers showing reduced looking toward social stimuli [39] and its high heritability.[40] Research has underscored the complex nature of attention differences in infants later diagnosed with autism. Lower attention to faces was found in 6-, 9-, and 12-month-olds later diagnosed when the caregiver spoke to or tickled the infant, but not during singing or toy play.[41] Unlike infant siblings without autism and neurotypical infants, those subsequently diagnosed with autism did not exhibit differential gaze toward their caregiver versus a stranger during interaction.[42] Another prospective study of 92 infant siblings and 26 low likelihood siblings found that toddlers later diagnosed with autism (n = 14) looked longer at a person when the interaction was predictable.[43]

Reduced responding to the child's own name is an aspect of social attention characteristic of autism in toddlers,[44,45] and is a pre-diagnostic marker with predictive power from 9 months strengthening thereafter,[46] though it might not be specific to autism until 24 months.[47] Joint attention occurs when a caregiver and child share their focus toward an object and is a cornerstone for language development.[48] In a prospective study of 482 infant siblings and 178 low likelihood infants, initiating joint attention (IJA) was found to be reduced in 12-

month-old infants who later progress to autism.[49] A smaller longitudinal study of 57 12-month-old infant siblings did not find reduced IJA in infants with later autism.[50] Another prospective study of 50 infant siblings showed 14-month-old infant siblings later diagnosed with autism had a lower frequency of IJA and reduced coordination between IJA and vocalizations.[51]

Twelve-month-old infant siblings later diagnosed with autism were found to exhibit a longer latency to shift attention away from a fear face.[52] Another longitudinal study that used the gap-overlap task with 83 infant siblings and 53 low likelihood infants reported asymmetric and prolonged attention disengagement to geometric stimuli in 12-month-old infants with later autism, with longer left-directed disengagement associated with higher irritability and difficulty to soothe.[53]

Prelinguistic development

Differences in prelinguistic development have been found for infants later diagnosed with autism. In the first year, infants transition from non-syllabic to syllabic vocalisations, with canonical syllables typically evident at about 7 months and increasing over the next several months. By 9-12 months, infants later diagnosed with autism have been found to produce fewer vocalisations, particularly canonical/speech-like vocalisations, and more frequent noncanonical/non-speech-like vocalisations.[54] Atypical vocalisation patterns, especially lower rate of canonical babbling, have been observed in infants with later autism and those with later language delay without autism.[55,56] Importantly, caregivers respond more to canonical/speech-like vocalisations, and contingent adult responses to infant vocalisations shape and refine babbling development.[57] Thus, early differences in vocal production could lead to reduced social feedback and downstream consequences for communication and language development in infants later diagnosed with autism. A consistent finding that distinguishes infant siblings who are subsequently diagnosed with autism is less frequent use of socially directed vocalisations.[58] Infants later diagnosed with autism have also been found to exhibit unusual crying, noted as early as 1 month of age.[59]

A distinct trajectory of gestural development has also been observed in infants later diagnosed with autism. From 8-14 months, infants later diagnosed with autism have been found to exhibit slower growth in use

of gestures, particularly deictic gestures (e.g., pointing) and gesture-vocal coordination, which distinguished them from neurotypical children, infant siblings without autism, and children with language delay.[60,61] Gesture use at 12 months of age has been found to be predictive of an autism diagnosis and associated with concurrent and later receptive and expressive language abilities.[62]

Affect, temperament, and social engagement

Although differences in affect and temperament have been found in 6–9-month-old infants later diagnosed with autism (e.g., increased negative affect and regulatory control),[63,64] findings across studies have been mixed potentially due to differences in methods used (e.g., parent report versus clinical observation).[65] A longitudinal study of 473 infant siblings and 176 low likelihood infants found that lower positive affect and lower attention-shifting predicted a later diagnosis of autism (n = 129), a profile that was stable from 6 to 24 months.[66] By 12-18 months, toddlers later diagnosed with autism were found to display lower positive affect and reduced smiling.[65-67] Reduced regulatory capacity and increased negative affect have been reported by 12 months and older[64] but are also found in toddlers later diagnosed with ADHD.[67,68] By 18-36 months, autistic toddlers have been found to exhibit increased neutral affect and reduced approach, positive anticipation, and attentional control, especially the ability to shift attention.[65,67,69,70]

Persistent differences in social engagement have been noted by 6 months, including reduced looking at a parent's face during interaction.[41] By 9 months, reduced eye gaze, facial expressions, gestures, and vocalizations during interaction were evident.[60] By 12 months, toddlers later diagnosed with autism have been found to fail to shift their attention to their caregiver's touch (or orient away),[71] and have lower dyadic synchrony, which was found to be correlated with later language abilities.[72]

Sensory sensitivity and habituation

Differences in sensory responses and interests fall into the domain of restricted interests/repetitive behaviours in the DSM-5 diagnostic criteria for autism spectrum disorder. Such differences can appear as either hypo- or hyper-sensitivity, and/or reduced or increased sensory exploration of the environment. Habituation is a decreasing response to repeated sensory stimuli, with subsequent recovery when a novel stimulus is presented.

Reduced rates of habituation can result in both apparent hyper-sensitivity (to repeated stimuli) and hyposensitivity (lack of increased response to a novel stimulus). Parental report, eye tracking and EEG studies have investigated sensory sensitivity and habituation in early autism.

Based on parent ratings, differences in sensory processing have been documented from 6 to 12 months onwards preceding a later diagnosis of autism and the presence of restricted and repetitive behaviours.[73,74,75] This association strengthens during the second year,[76,77] and occurs in both social and non-social contexts.[78] EEG and eye tracking have been used to establish the latency and strength of sensory responses to repeated stimuli within the first year. These studies have established associations with later diagnosis and/or autism-related behaviours,[19,79-81] in each of the visual,[79,81] auditory,[19] and tactile domains,[80] and a potential lack of sensitivity to inter-sensory synchrony, implicating atypical sensory integration.[82] Thus, sensory sensitivities can be detected from at least 8-10 months using several methods. Such sensitivities become more strongly predictive of an autism diagnosis between 12-24 months and increasingly resemble diagnostic criteria with some exceptions.[79,81]

Motor abilities, toy play, and restrictive/repetitive behaviours

Acquisition of motor skills affords opportunities for object exploration and interactive play that support cognitive and language development. By 6-9 months, delayed sitting, pull-to-sit, reach to grasp and goal-directed reaching have been observed in infants with later autism. Fine and gross motor delays are evident by 12 months and onward and predict later expressive and receptive language abilities.[83,84] Difficulties in postural control and frequent head movements appear early and are persistent.[85]

Differences in object use have been observed in infants subsequently diagnosed with autism. While no differences were observed in ability to predict movements of occluded objects,[86] differences in exploratory behaviours were observed in 10-month-old infants.[87] By 18-24 months, reduced exploratory toy play and unusual toy interests have been observed.[88]

Repetitive behaviours have been noted by 9 months, particularly unusual visual inspection of objects.[89] By 12 months, infants later diagnosed with autism displayed more frequent stereotyped motor mannerisms,

repetitive object use and head movements.[90] Self-injurious behaviours have been observed in infant siblings by 9 months, although these were not found to be specific to toddlers later diagnosed with autism.[90]

Individual-level prediction

Screening approaches based on early behavioural signs have included caregiver questionnaires and clinical observation (table 1). Parent report of behavioural features derived from the First Year Inventory identified 12-month-old infant siblings with a later autism diagnosis with sensitivity of 0.71 and specificity of 0.72.[91] In a sample of infants for whom there were existing parent or professional concerns, the Early Screening for Autism and Communication Disorders questionnaire identified later autism with 0.86 sensitivity and 0.82 specificity.[92] In a study of 9-month-old siblings, the Autism Parent Screen for Infants identified infants with later autism with 0.42 sensitivity and 0.90 specificity.[93] In a large sample comprised of infant siblings and low-likelihood infants who were assessed using the Autism Observation Scale for Infants, a structured clinical observation, sensitivity and specificity values changed from 6- to 12-months of age from 0.57/0.51 to 0.52/0.74 respectively.[94]

Translation of research into screening tools for clinical practice

While much progress has been made in identifying differences in early brain development, health conditions, and behavioural characteristics associated with a later diagnosis of autism, the challenge ahead is to translate these scientific findings into validated screening tools that can be used in clinical practice. Most of the work to date has identified potential biomarkers and behavioural precursors that discriminate groups of infants with or without a later diagnosis of autism, whereas fewer studies have investigated the ability of these markers for individual prediction of autism, a requirement for a screening tool.

Notably, most studies to date have focused on infant siblings or those for whom there was an existing professional concern. These populations comprise subsets of the more heterogeneous general population of infants for whom a screening tool would be used in practice. Head-to-head comparisons of different types of biomarkers (e.g., MRI versus EEG) are difficult because most biomarkers are studied in isolation, and only a few studies have compared or combined different biomarkers at similar ages [22,25,38]. Comparison groups of infants have often been chosen because they have no known factors associated with autism ("low likelihood

infants"), which likely inflates accuracy of prediction estimates. Many studies suffer from small sample sizes that lack diversity, which will make replication in the broader population difficult. Sample sizes in most studies have precluded reliable estimates of the effects of sex, race, and ethnicity. Few studies have examined the effects of co-occurring psychiatric conditions (e.g., ADHD) on prediction accuracy.[47,80] Moreover, most studies have gathered data in academic research labs with a relatively narrow subset of racially, ethnically, and linguistically homogeneous and high-income families, and fewer studies have been conducted in the settings within which screening would be expected to occur, such as primary paediatric clinics or other community settings (although see [39,45,70]). Finally, recent screening approaches based on machine learning algorithms will require replication based on larger, independent samples.

Conclusions and future directions

Research findings to date suggest that a combination of infant measures offers stronger prediction of diagnostic outcome than a single measure, both within[95] and across types of measures. For example, there is improved prediction of autism when the N290 ERP component is combined with autism polygenic scores.[22] Studies of digital phenotypes based on computer vision find that autism prediction improves when multiple behavioral phenotypes (e.g., distinct gaze features) are combined.[45,39] Future studies using machine learning and hybrid statistical approaches based on interpretable components will allow us to discover the best weighting of combinations of variables to predict later diagnosis. Independent replication of such prediction strategies is important.

A challenge that remains to be addressed is that emerging autism is frequently accompanied by co-occurring medical conditions. Establishing which of these are causal or contributary, and which are consequential, remains a challenge for the future. For example, dysregulation of sleep is a widely reported co-occurring condition that could either be a parallel consequence of atypical brain function, or causal/contributory in that poor quality sleep is known to affect cognition, attention, and temperament, potentially compounding other difficulties.

A related question is the degree to which the early biomarkers are specific to a later autism outcome. Comparisons between infants at familial risk for autism versus ADHD are helping to address this issue. One such study reported that responses to the infant's own name did not become a marker specific to autism outcome until 24 months.[47] Another study reported that within a group of infant siblings, markers predicting autism-related behaviours differed from those of mid-childhood ADHD and anxiety-related behaviours; increased infant activity levels and lower inhibitory control were associated with later ADHD-related behaviours and not autism or anxiety, but increased fearfulness and shyness in infancy were associated with mid-childhood anxiety- and autism-related behaviours.[96]

A paradox remains that while several pre- and peri-natal causal factors have been implicated in autism, it is not until 18-24 months that behavioural features cohere into a stable diagnosable autism syndrome. However, this prolonged trajectory gives hope for identifying specific intervention domains during infancy and potentially promoting developmental trajectories that could reduce challenges associated with autism. Clinical trials of caregiver-delivered interventions in infant siblings, or following early screening, have been reported with encouraging results.[23,97-98] Interventions designed to promote cognitive development and social engagement are a promising avenue for future work. This work should include ethical, practical, and clinical considerations regarding the benefits versus risks of very early identification and intervention, especially for asymptomatic infants.[99]

Substantial challenges remain to be addressed before current findings on infant biomarkers and predictors can be translated into scalable and feasible screening tools that can be used within health systems. Most notably, most of the research has been conducted with infant siblings, a specific subgroup among the autism population. A question remains whether different causal routes to autism have the same predictors in infancy, or whether the described phenomenon is specific to familial polygenic risk. This question has begun to be investigated with cohorts recruited from the general population with no known genetic risk factor or prior concern, [39,45,70] as well as those with genetic syndromes, such as fragile-X, tuberous sclerosis, and

neurofibromatosis 1 (NF1). For example, in one study of infants with NF1, slower neural detection of repeated auditory stimuli was correlated with autism-related behaviours at 14 months.[100]

Addressing the substantial heterogeneity among the autism population will be essential for translation of research on early infant markers to practical screening approaches. This includes the development of early screening approaches that have been validated on diverse populations in terms of sex, race, ethnicity, and income which can be feasibly used in low- and middle-income countries. Embedding culturally anchored screening tools within a clinical care pathway that considers feasibility, acceptability, and usability and links screening to referral, diagnosis, and services is essential. Finally, while the broad goal of linking infant screening to interventions and services that improve quality of life is commendable, future work should consider what safeguards would be needed to mitigate the potential risks of such a strategy.

In conclusion, there is encouraging evidence that prediction of later autism in infants is possible. This goal will be accelerated by the advent of new biomarker technologies and assays used in the context of large infant longitudinal studies that simultaneously track the early development of autism at multiple levels of analysis (genetic, brain, health, behaviour). Key factors in future success include the need for studies of more diverse populations of infants and an implementation science framework involving a variety of stakeholders, including providers, caregivers, and self-advocates, which will ensure that the screening tools can be effectively used in practice, linked to beneficial infant-toddler intervention services, and ultimately improve quality of life for individuals on the autism spectrum.

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Search strategy and selection criteria

We searched PubMed (Medline) using broad and exploded search terms for review concepts including “infant” AND “autism spectrum disorder” AND “prediction” (see detailed search strategy below). For specific sections, additional search terms included “magnetic resonance imaging” OR “health”, OR “behaviour”, for example. We also searched the references within the selected papers for relevant articles. Articles included in this review were published in peer-reviewed English-language journals between Jan 1, 2016, and June 1, 2022. Thus, the review focused on recently published literature with a few exceptions when earlier papers were necessary for context. We included only prospective longitudinal studies, as well as retrospective studies of medical records, of participants during the infant-toddler period before an established autism diagnosis using DSM-5 criteria. For the current review, studies that aimed to establish the use of novel biomarker/screening approaches, centred around infant-toddler behaviour, physical health, brain structure and function, and development were included. The final reference list was compiled and synthesized based on relevance to the content covered in this review.

Search strategy
((((("autism spectrum disorder"[MeSH Terms] OR "autistic disorder"[MeSH Terms] OR "autism spectrum disorder"[Title/Abstract] OR "autism"[Title/Abstract] OR "autistic"[Title/Abstract] OR "asd"[Title/Abstract]) AND ("infant"[MeSH Terms] OR "infant"[Title/Abstract] OR "infants"[Title/Abstract] OR "toddler"[Title/Abstract] OR "toddlers"[Title/Abstract] OR "early child"[Title/Abstract]) AND ("brain imaging"[Title/Abstract] OR "magnetic resonance imaging"[Title/Abstract] OR "mri"[Title/Abstract] OR "neuroimaging"[MeSH Terms] OR "neuroimaging"[Title/Abstract] OR "electroencephalography"[MeSH Terms] OR "electroencephalography"[Title/Abstract] OR "eeg"[Title/Abstract] OR "evoked potentials"[MeSH Terms] OR "erp"[Title/Abstract] OR "evoked"[Title/Abstract] OR "magnetoencephalography"[MeSH Terms] OR "magnetoencephalography"[Title/Abstract] OR "meg"[Title/Abstract] OR "spectroscopy, near infrared"[MeSH Terms] OR "fnirs"[Title/Abstract] OR "behaviour"[Title/Abstract] OR "behaviour and behaviour Mechanisms"[MeSH Terms] OR "behav*"[Title/Abstract] OR "eye"[MeSH Terms] OR "eye"[Title/Abstract] OR "predict*"[Title/Abstract] OR "detect*"[Title/Abstract] OR "classif*"[Title/Abstract] OR "accuracy"[Title/Abstract] OR "sensitivity"[Title/Abstract] OR "specificity"[Title/Abstract] OR "electronic health records"[MeSH Terms] OR "medical"[Title/Abstract] OR "health"[Title/Abstract] OR "early medical intervention"[MeSH Terms]))

Author contributions

Dawson's contributions included conceptualization, funding acquisition, supervision, writing – original draft, review, and final editing. Johnson's contributions included conceptualization, funding acquisition, supervision, writing – original draft, review, and final editing. Rieder's contributions included conceptualization, data curation, and writing – review and final editing.

Declaration of Interests

Dawson is on the Scientific Advisory Boards of Akili Interactive, Inc., Zynerba, Nonverbal Learning Disability Project, and Tris Pharma; is a consultant to Apple Inc., Gerson Lehrman Group, and Guidepoint Global, Inc.; and receives book royalties from Guilford Press and Springer Nature. Dawson has developed technology, data, and/or products that have been licensed to Apple, Inc. and Cryocell, Inc. Johnson receives book royalties from Wiley-Blackwell and Oxford University Press. Rieder and Sturdivant have no conflicts of interests to declare.

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Figure 1. A 1-month-old infant looks at a face stimulus during a home-based study using functional near infrared spectroscopy to measure increases and decreases in regional neural activity.

Table 1. Recent studies providing individual-level prediction of later autism in infants ≤ 12 months [a]

Predictor type	Authors, date	Study type	Measure used for prediction	Comparison population with infants diagnosed with autism	Age	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
MRI	Shen et al., 2017 [11]	Prospective longitudinal multisite	Algorithm using extra-axial cerebrospinal fluid, cerebral volume, age, and sex	Infant siblings without later autism	6 mos.	0.66	.68	-	-
	Hazlett et al., 2017 [4]	Prospective longitudinal multisite	Surface area growth	Infant siblings without later autism	6-12 mos.	0.88	0.95	0.81	0.97
	Emerson et al., 2017 [13]	Prospective longitudinal multisite	Whole-brain resting-state fMRI	Infant siblings without later autism	6 mos.	0.82	1.00	-	-
EEG	Miron et al., 2016 [26]	Retrospective from medical records	Prolonged auditory brainstem response	Cased-matched based on birth week, gender, and age comparison group of children who were not diagnosed with autism	3 mos.	0.70	0.80	0.78	0.73
	Bosl et al., 2018 [15]	Prospective longitudinal	EEG nonlinear features (e.g., entropy)	Infant siblings combined with low likelihood infants [b]	3 mos.	.0.82	0.99	0.97	N.A.
	Gabard-Durnam et al., 2019 [16]	Prospective longitudinal	Longitudinal frontal EEG spectral power	Infant siblings without later autism	3-12 mos.	0.82	0.86	0.72	0.92
Caregiver survey	Lee et al., 2019 [91]	Prospective longitudinal	First Year Inventory	Infant siblings without later autism	12 mos.	0.34	0.91	0.67	0.74
	Wetherby et al., 2021 [92]	Case-control comparison	Early Screening for Autism and Communication Disorder	Infants screened in primary care for language delay and infants with prior concern and/or infant sibling who did not receive an autism diagnosis	12-17 mos.	0.86	0.82	0.64	0.94
	Sacrey et al., 2021 [93]	Prospective longitudinal	Autism Parent Screen for Infants	Infant siblings without later autism and low likelihood infants [b]	9 mos.	0.42	0.90	0.72	0.72
Clinical observation	Zwaigenbaum et al., 2021 [94]	Prospective longitudinal	Autism Observation Scale for Infants	Infant siblings without later autism	6 mos. 9 mos.	0.57 0.60	0.51 0.53	0.26	0.80

				and low likelihood infants [b]	12 mos.	0.52	0.74	0.35 0.43	0.76 0.80

[a] This list of studies is not a systematic review of all studies that have examined individual-prediction level statistics in infants later diagnosed with autism. The table reflects studies conducted from 2016-June 2022 covered in this article.
[b] Low likelihood infants are those without a family history of autism.