Prediction of autism in infants: progress and challenges

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Autism spectrum disorder (henceforth autism) is a neurodevelopmental condition that can be reliably diagnosed in children by age 18–24 months. Prospective longitudinal studies of infants aged 1 year and younger 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 that use 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 infants younger than 1 year who received a later diagnosis of autism have also showed 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, gestures, affect, temperament, social engagement, sensory processing, and motor abilities. Although research findings offer insight on promising screening approaches for predicting autism in infants, individual-level predictions remain a future goal. Multiple scientific challenges and ethical questions remain to be addressed to translate research on early brain-based and behavioural predictors of autism into feasible and reliable screening tools for clinical practice.

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Introduction

Autism spectrum disorder (henceforth autism) is a neurodevelopmental condition—characterised by qualitative differences in social communication abilities, together with restricted interests and repetitive behaviours—that can be reliably diagnosed in children by age 18–24 months. Technological and scientific advances have led to an improved understanding of brain and behavioural development in infants aged 12 months and younger who are later diagnosed with autism. Research suggests that progress is being made in the detection of autism during infancy—a period of rapid brain development when interventions might have increased potential to influence later outcomes. However, challenges associated with individual-level predictions, substantial implementation barriers of screening tools, and the heterogeneity of autism should be addressed before scientific research on prediction of autism in infants can be fully translated into clinical practice. Furthermore, most studies to date have prospectively followed up infants who have an older sibling diagnosed with autism (henceforth, for brevity, referred to as infant siblings), who have been shown to have an increased likelihood of being diagnosed with autism 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 (henceforth low-likelihood infants). Although this study design has been a powerful approach, the generalisability of findings from this subgroup to the broader population of individuals with autism remains to be established.

In this Review, we summarise the latest advances and ongoing challenges in prediction of autism during infancy, with a focus on three domains: brain development, physical health, and behavioural development. We first describe findings from studies published primarily after 2015, and then discuss the challenges that remain to be addressed in the future to facilitate translation of research findings into validated tools for clinical application.

Brain-based biomarkers

Several prospective longitudinal studies of potential predictive brain-based biomarkers have shown 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 brain structure and function in infants, each of which provides a unique perspective on brain development (panel). MRI findings, together with preclinical research on syndromic autism in animal models, implicate differences in neural progenitor proliferation and neurogenesis.[2] Alterations in the inhibitory–excitatory balance at the neuronal and synaptic levels might also influence the early development of functional 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 interacts with the environment probably further shape the development of experience-dependent neural circuitry.

MRI

Prospective MRI studies have identified multiple differences in early brain development of infants later diagnosed with autism. Brain overgrowth (ie, increased cerebral cortical volume) in the first and second years of postnatal life occurs in infant siblings subsequently diagnosed with autism.[4] Compared with infant siblings who were not diagnosed with autism, those with later autism exhibit accelerated growth of the cortical surface area from age 6–12 months, especially of the occipital, temporal, and frontal lobe regions, which precedes brain overgrowth occurring between age 12 months and 24 months.[4] An accelerated growth of the amygdala was seen in infant siblings aged 6 months and 12 months subsequently diagnosed with autism, compared with infants with fragile X syndrome, infant siblings without autism, and infants 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 infant siblings

Panel: Brain-based biomarkers used in infant studies of autism

MRI

Structural MRI

Structural MRI uses magnetic fields and radio waves to produce two-dimensional or three-dimensional structural images of the brain, yielding measures such as total brain volume, cortical surface area, cortical thickness, gyrification, and subcortical structural volumes.

Diffusion tensor imaging

Diffusion tensor imaging is a technique for measuring white matter tracts in the brain by using the direction and motion of water molecules.

Fractional anisotropy

Fractional anisotropy is used in diffusion tensor imaging research to reflect the integrity of white matter by assessing the degree of myelination and axonal density, with values ranging from 0 (weak) to 1 (strong).

Extra-axial CSF volume

Extra-axial CSF can be measured via MRI and reflects excesses in the CSF amount in the subarachnoid space in the brain.

Functional MRI

Functional MRI measures changes in oxygen concentrations in blood in specific brain regions during resting state or in response to time-locked stimulus presentations by use of blood oxygenation level dependent imaging to assess regional brain activity.

EEG

Spectral EEG power analysis

Spectral EEG power analysis can be assessed during resting state or presentation of various stimuli. It quantifies power in each frequency band (delta, theta, alpha, beta, and gamma) and can be given as absolute or relative power (ie, absolute power in each frequency band as a percentage of the sum of all frequencies).

Event-related potentials

Event-related potentials reflect the electrophysiological response to a specific stimulus, which is repeated and then averaged to show components time-locked to the stimulus presentation that vary in latency and amplitude.

EEG connectivity

EEG connectivity can be assessed during resting state or presentation of various stimuli. It quantifies the rhythmic neuronal interactions and synchronisation of EEG signals collected at different sites across the scalp. Examples of measures of EEG functional connectivity include coherence (a measure of phase synchrony between a pair of signals) and phase slope index (a measure of the consistency of the direction of the change in the phase difference across frequencies).

EEG complexity

EEG complexity can be measured via multiscale entropy, a measure of the temporal irregularity or complexity of the EEG time series over different time scales.

Detrended fluctuation analysis

Detrended fluctuation analysis is a measure of EEG persistence over time, reflected in the fluctuation of the non-stationary time series in the temporal domain.

Microstates

EEG microstates are a dynamic assessment of the spatial and temporal distribution of the electrical signal across the scalp electrodes, defining a brief quasi-stable state in any frequency band.

Auditory brainstem response

Auditory brainstem response, also referred to as brainstem auditory evoked potentials, is a measure of electrical activity in the brainstem auditory pathway assessed by electrodes placed on the scalp in response to repeated simple auditory stimuli.

Near-infrared spectroscopy

Regional haemodynamic responses

Functional near-infrared spectroscopy is a non-invasive technique that uses near-infrared light sources and detectors to measure haemodynamic responses (eg, oxygenation) in the brain reflecting increases and decreases in regional neural activity.

aged 4–6 months (regardless of later diagnosis).[6] In a separate longitudinal study, when infant siblings later diagnosed with autism (n=86) were compared with infant siblings with early language delay (n=41) and with infants who did not receive a diagnosis of autism (n=255) or who did not exhibit delays in language development (n=143), results showed that, at age 12 months, infants with later autism had enlarged subcortical structures compared with infants with later language delay.[7] A prospective longitudinal study comparing infant siblings (n=270) with low-likelihood infants (n=108) found that enlarged corpus callosum at age 6 months predicted later autism-related behaviours. Differences in corpus callosum thickness between children with and without a diagnosis of autism diminished by age 2 years, suggesting a dynamic process of early development of the corpus callosum.[8]

In a study of 92 infant siblings, measurement of fractional anisotropy (a measure reflecting the degree of myelination and axonal density) showed differences in the developmental trajectory of white matter between infants who were later diagnosed with autism and those who were not; in infants with autism, development of the white matter fibre tract was characterised by increased fractional anisotropy at age 6 months followed by slower change over time in fractional anisotropy through age 24 months.[9] A study of 116 infant siblings reported differences in white matter network efficiency in siblings aged 6 months and later diagnosed with autism.[10] Variations in white matter development in distinct brain structures in infants

	Study type	Measure used for prediction	Comparison group	Age	Sensitivity	Specificity	Positive predictive value	Negative predictive value
MRI								
Shen et al (2017)[11]	Prospective longitudinal multi-site	Algorithm using extra-axial CSF, cerebral volume, age, and sex	Infant siblings without later autism	6 months	0·66	0·68	..	..
Emerson et al (2017)[13]	Prospective longitudinal multi-site	Whole-brain resting-state functional MRI	Infant siblings without later autism	6 months	0·82	1·00	..	..
Hazlett et al (2017)[4]	Prospective longitudinal multi-site	Surface area growth	Infant siblings without later autism	6–12 months	0·88	0·95	0·81	0·97
EEG								
Gabard-Durnam et al (2019)[14]	Prospective longitudinal	Frontal EEG spectral power	Infant siblings without later autism	3–12 months	0·82	0·86	0·72	0·92
Bosl et al (2018)[15]	Prospective longitudinal	EEG non-linear features (eg, entropy)	Infant siblings without later autism and low-likelihood infants	3 months	0·82	0·99	0·97	..
Miron et al (2016)[16]	Retrospective from medical records	Extended auditory brainstem response	Infants without later autism were case matched on the basis of birth week, sex, and age	0–3 months	0·70	0·80	0·78	0·73
Caregiver survey								
Wetherby et al (2021)[17]	Case-control comparison	Early Screening for Autism and Communication Disorder	Infants screened for language delay in primary care, infants referred for previous concern for autism, and infant siblings without later autism	12–17 months	0·86	0·82	0·64	0·94
Sacrey et al (2021)[18]	Prospective longitudinal	Autism Parent Screen for Infants	Infant siblings without later autism and low-likelihood infants	9 months	0·42	0·90	0·72	0·72
Lee et al (2019)[19]	Prospective longitudinal	First Year Inventory	Infant siblings without later autism	12 months	0·34	0·91	0·67	0·74
Clinical observation								
Zwaigenbaum et al (2021)[20]	Prospective longitudinal	Autism Observation Scale for Infants	Infant siblings without later autism and low-likelihood infants	6 months, 9 months, and 12 months	0·57, 0·60, and 0·52	0·51, 0·53, and 0·74	0·26, 0·35, and 0·43	0·80, 0·76, and 0·80

Studies are listed according to year of publication. Only studies identified as per our search strategy and selection criteria are included. Infant siblings are infants who have an older sibling diagnosed with autism and who therefore have a higher likelihood of a diagnosis of autism because of genetic factors. Low-likelihood infants are infants with no family history of autism.

Table: **Studies providing individual-level predictions of later autism in infants aged 12 months or younger**

subsequently diagnosed with autism have been associated 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 age 6 months predicted later autism and remained elevated through age 24 months.[11] CSF contains growth factors that influence neuronal proliferation and has been hypothesised to play a role in clearing metabolites, including amyloid β and pro-inflammatory cytokines, both of which can affect brain function.

A study of resting-state functional MRI (fMRI) during sleep found disruptions in thalamocortical connectivity and language-related networks by age 1·5 months in infant siblings, regardless of later diagnosis.[12] Infant siblings aged 6 months with atypical patterns of functional connectivity based on fMRI were more likely to be diagnosed with autism at age 2 years than infant siblings without a diagnosis of autism.[13]

Individual-level predictions based on MRI

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 the accuracy of individual-level predictions (table). At age 6 months, an algorithm combining measures of extra-axial CSF, brain volume, age, and sex predicted which infant siblings were later diagnosed with autism with a sensitivity of 0·66 and a specificity of 0·68.[11] By use of cross-validated machine learning, whole-brain resting-state fMRI at age 6 months predicted later autism in infant siblings with sensitivity of 0·82 and sensitivity of 1·00.[13] By use of machine learning, measures of brain surface area at age 6–12 months predicted diagnostic outcomes in infant siblings with a sensitivity of 0·88 and a specificity of 0·95.[4]

Electrophysiological biomarkers

Recordings of auditory brainstem responses, spontaneous EEG, and event-related potentials (ERP) in infants have shown differences in timing, amplitude, and spectral power that could serve as brain-based biomarkers of autism. Retrospective analysis of routinely collected data on auditory brainstem responses in a hearing screening of 139 154 neonates (321 later diagnosed with autism) has shown prolongations of the auditory brainstem response

phase and wave V-negative latency in neonates later diagnosed with autism.[21] Research using machine learning to analyse spontaneous EEG from 99 infant siblings and 89 low-likelihood infants found that EEG complexity[15] and longitudinal trajectories of multiple power spectral densities predicted later autism.[14] Although a study reported that increased EEG connectivity in the alpha frequency band in infants aged 14 months was associated with a later diagnosis of autism,[22] a separate study attempting to replicate these observations found that an increased alpha EEG connectivity was only associated with a degree of restricted interests and repetitive behaviours.[23] Among infants aged 8 months (116 infant siblings and 27 low-likelihood infants), increased cortical reactivity to repeated tones (reflected in reduced suppression of 40–60 Hz evoked gamma and increased 10–20 Hz inter-trial coherence) was associated with a later diagnosis of autism.[24] Infant siblings aged 6 months who were later diagnosed with autism were found to have less robust ERPs to facial expressions and shorter epochs of visual attention to faces than infants without later autism.[25] Infants aged 6–10 months subsequently diagnosed with autism showed lower inter-trial coherence in the theta frequency band during visual face processing.[26] Infants aged 8 months who were later diagnosed with autism exhibited a diminished N290 ERP, a component that has been shown to be responsive to face stimuli.[27] Prediction of later autism improved when adding autism polygenic scores as an independent variable to the logistic model that assessed prediction based on the N290 latency to face and non-face stimuli.[27]

In a small randomised clinical trial including infant siblings aged 9–11 months (n=33), EEG measures were used to assess the effects of an early intervention designed to promote social engagement during caregiver–infant interactions. Infant siblings who received the caregiver-delivered 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 infant siblings who did not receive the intervention.[28]

In a study of infants aged 8 months (91 infant siblings and 40 low-likelihood infants), shorter duration of EEG microstates related to social attention predicted later diagnosis of autism.[29] 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 associated with a subsequent diagnosis of autism.[30]

Individual-level predictions based on EEG

Studies that have examined individual-level predictions suggest that electrophysiological biomarkers show promise as a method for early screening, as they have high sensitivity and specificity as early as in the first 3 months of life (table). In a longitudinal study of both siblings and low-likelihood infants, EEG power (particularly in the frequency bands delta and gamma) trajectories from 3–12 months reliably predicted infant siblings later diagnosed with autism with a sensitivity of 0·82 and a specificity of 0·86.[14] Furthermore, as early as age 3 months, an algorithm that included non-linear EEG features (eg, entropy and detrended fluctuation analysis) predicted which infant siblings would later be diagnosed with autism versus a combined group of infant siblings and low-likelihood infants who did not receive a diagnosis of autism with a sensitivity of 0·82 and a specificity of 0·99.[15] In a retrospective study of clinical auditory brainstem response recordings taken at 0–3 months from 30 infants later diagnosed with autism and 30 case-matched controls, a pattern of extended auditory brainstem response wave-V latency distinguished the two groups with a sensitivity of 0·70 and a specificity of 0·80.[16]

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

Near-infrared spectroscopy

Albeit with lower spatial resolution, NIRS has the advantage over fMRI of being readily usable in infants and toddlers while they are engaged in activities (figure). In a NIRS study of infants aged 5 months (16 infant siblings and 13 low-likelihood infants), brain responses to viewing social videos (eg, actions made by a female actor) were compared with those elicited by non-social images (eg, cars and helicopters).[31] Low-likelihood infants showed greater activation of the right posterior temporal cortex than infant siblings.[31] In a separate analysis using NIRS with infants aged 4–6 months (20 infant siblings and 16 low-likelihood infants), infants later diagnosed with autism showed

reduced activation to the social videos across the inferior frontal and posterior temporal cortical regions, and reduced activation to vocal sounds and enhanced activation to environmental noises across the left temporal regions.[32] In another NIRS study of 32 infants aged 6 months (of which 14 were infant siblings), infants later diagnosed with autism had reduced brain responses to speech sounds in bilateral temporal and frontal cortical regions.[33]

To our knowledge, no studies providing individual-level predictions based on NIRS have been published.

Early physical health conditions

Individuals with autism have higher rates of co-occurring medical conditions than individuals without a diagnosis of autism, and many of these conditions are present in the first year of life before diagnosis.[34] 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 they are a potential target for early intervention.

Among the early medical factors associated with autism are sex-specific differences in head circumference (both larger and smaller circumference), preterm delivery and low birthweight, perinatal stroke due to hypoxia, and presence of congenital malformations or genetic syndromes.[35,36] The odds of a diagnosis of autism are estimated to be 3·3 times higher in children born preterm than in the general population.[37] Epilepsy, including infantile spasms, is more prevalent in individuals diagnosed with autism than in the general population.[38,39] In a prospective study of 432 infants aged 6–12 months (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 caregiver-reported sleep-onset problems, which were associated with differences in hippocampal volume trajectories.[40]

Retrospective studies using electronic health records 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 of 29 929 patients found that infants younger than 1 year and later diagnosed with autism (n=343) were more than three times more likely to visit an ophthalmologist, gastroenterologist, or neurologist than those without a subsequent diagnosis of autism.[34] Infants later diagnosed with autism were also more likely to have nausea or vomiting, or both, and abdominal pain.[34] Another study based on medical records (3911 cases with autism and 38 609 controls) found that, in the first 3 years of life, increased rates of neurological; nutrition-related; genetic; ear, nose, and throat; and sleep conditions were associated with an increased likelihood of a subsequent diagnosis of autism.[41] Importantly, infants later diagnosed with autism show distinct patterns of early medical conditions compared with infants with other neurodevelopmental diseases, such as attention-deficit hyperactivity disorder (ADHD).[34]

Autism prediction models are being developed by leveraging large datasets from electronic health records and machine learning of health care data collected during routine visits during infancy.[34] For example, data from electronic health records were used to cluster children on the basis of their medical conditions before a diagnosis of autism and predict an eventual diagnosis.[41] Another study used machine learning based on early medical conditions to predict later autism status with encouraging results, which remain to be replicated in future studies.[42]

Early behavioural markers

A wide range of behavioural markers of autism can be observed in infants aged 12 months and younger. These markers include differences in attention, development of prelinguistic communication, affect, temperament, social engagement, sensory sensitivity and habituation, motor abilities, toy play, and restrictive and 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 (eg, 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 observed in toddlers diagnosed with autism,[43] has been hypothesised to have downstream effects on social development,[44] and is strongly influenced by genetic factors.[45] Research has underscored the complex nature of attention differences in infants later diagnosed with autism. Lower attention to faces was found in infants aged 6, 9, and 12 months later diagnosed with autism when the caregiver spoke to, or tickled, the infant, but not during singing or toy play.[46] Unlike infant siblings without autism and neurotypical infants, those subsequently diagnosed with autism did not exhibit differential gaze towards their caregiver versus a stranger during interaction.[47] 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.[48]

Reduced responding to children's own names is an aspect of social attention characteristic of autism in toddlers,[49,50] and is a prediagnostic marker with predictive power established from age 9 months and strengthening in later infancy,[51] although reduced response to one's name might not be a specific predictor of autism until age 24 months.[52] Joint attention occurs when a caregiver and a child share their focus towards an object, and is a cornerstone of language development.[53] In a prospective study of 482 infant siblings and 178 low-likelihood infants, initiating joint attention was reduced in infants aged

12 months who later progressed to autism.[54] However, a smaller longitudinal study of 57 infant siblings aged 12 months did not find reduced initiating joint attention in infants with later autism.[55] Another prospective study of 50 infant siblings showed that infant siblings aged 14 months and later diagnosed with autism had a lower frequency of initiating joint attention behaviours and reduced coordination of initiating joint attention behaviours with vocalisations compared with infant siblings without a diagnosis of autism.[56]

Infant siblings aged 12 months and later diagnosed with autism exhibit an increased latency to shift attention away from a fearful face.[57] Another longitudinal study of 83 infant siblings and 53 low-likelihood infants reported asymmetric and extended attention disengagement from geometric stimuli in infants aged 12 months and with later autism, with longer left-directed disengagement associated with higher irritability and difficulty to soothe.[58]

Development of prelinguistic communication

Differences in the development of prelinguistic communication have been found between infants later diagnosed with autism and those without autism. In the first year of life, infants transition from non-syllabic to syllabic vocalisations, with canonical syllables typically evident at about age 7 months and increasing during the following several months. By age 9–12 months, infants later diagnosed with autism produce fewer vocalisations, particularly canonical (speech-like) vocalisations, and more frequent non-canonical (non-speech-like) vocalisations.[59] Atypical vocalisation patterns, especially reduced rates of canonical babbling, have been observed in infants with later autism and in those without autism but with later language delay.[60,61] Importantly, caregivers are more likely to respond to canonical vocalisations, and adult responses to infant vocalisations shape and refine babbling development.[62] 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 characterises infant siblings subsequently diagnosed with autism is the less frequent use of socially directed vocalisations (ie, vocalisations used for communicative purposes).[63] Infants later diagnosed with autism have also been found to exhibit unusual crying, noted as early as at age 1 month.[64]

A distinct trajectory of gestural development has also been observed in infants later diagnosed with autism. From age 8–14 months, infants later diagnosed with autism exhibit reduced use of gestures, particularly deictic gestures (eg, pointing) and gestural–vocal coordination, which distinguished them from neurotypical children, infant siblings without autism, and children with language delay.[65,66] Gesture use at age 12 months is predictive of a diagnosis of autism and associated with expressive language abilities at age 12 months as well as with later language abilities.[67]

Affect, temperament, and social engagement

Although differences in affective expressions and temperament have been found in infants aged 6–9 months later diagnosed with autism (eg, increased negative affect and regulatory control),[68,69] findings across studies have varied, potentially due to differences in methods (eg, caregiver report *vs* clinical observation).[70] A longitudinal study of 473 infant siblings and 176 low-likelihood infants found that caregiver-report of lower positive affect and lower attention-shifting predicted a later diagnosis of autism (n=129), a profile that was stable from 6 months to 24 months.[71] By 12–18 months, toddlers later diagnosed with autism were found to display lower positive affective expression and reduced smiling.[70–72] Reduced regulatory capacity and increased negative affect based on caregiver report and clinical observation have been reported in infants aged 12 months and older[69] but have also been found in toddlers later diagnosed with ADHD.[72,73] By 18–36 months, toddlers with autism exhibit increased neutral affect, and reduced social approach behaviour, positive anticipation, and attentional control, especially the ability to shift attention on the basis of caregiver report and clinical observation.[70,72,74,75]

Persistent differences in social engagement have been observed by age 6 months infants later diagnosed with autism, including reduced looking at a caregiver's face during interaction.[46] By age 9 months, reduced eye gaze, facial expressions, gestures, and vocalisations during interaction have been observed in infants later diagnosed with autism.[65] By age 12 months, toddlers later diagnosed with autism have been observed to not shift their attention to their caregiver's touch (or orient away),[76] and—correlated with later language abilities—to have lower dyadic synchrony.[77]

Sensory sensitivity and habituation

In the diagnostic criteria for autism of the *Diagnostic and Statistical Manual of Mental Disorders* (also known as DSM-5), differences in sensory responses and interests fall into the domain of restricted interests and repetitive behaviours. Such differences can appear as either hyposensitivity to repeated stimuli or hypersensitivity (increased response to a novel stimulus), or as 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 either apparent hypersensitivity or hyposensitivity. Sensory sensitivity and habituation in children with early autism have been investigated through caregiver reports, eye tracking, and EEG studies.

On the basis of caregiver ratings, differences in sensory processing have been documented in infants from age 6–12 months onwards, preceding a later diagnosis of autism and the presence of restricted and repetitive behaviours.[78–80] This association strengthens during the second year of life,[81,82] and occurs in both social and

non-social contexts.[83] EEG studies and eye tracking have been used to establish the latency and strength of sensory responses to repeated stimuli in the first year of life. These studies have established associations with later diagnosis or autism-related behaviours, or both,[24,84–86] in each of the visual,[84,86] auditory,[24] and tactile domains,[85] and a potential absence of sensitivity to intersensory synchrony, implicating atypical sensory integration.[87] Thus, sensory sensitivities can be detected from at least age 8–10 months by use of several methods. Such sensitivities become more strongly predictive of a diagnosis of autism between age 12–24 months and increasingly resemble behaviours described in the autism diagnostic criterion: hypersensitity to sensory input.[84,86]

Motor abilities, toy play, and restrictive and repetitive behaviours

In infants, the acquisition of motor skills affords opportunities for object exploration and interactive play that support cognitive and language development. By age 6–9 months, delayed sitting, pull-to-sit, reach-to-grasp, and goal-directed reaching have been observed in infants with later autism.[88] Fine and gross motor delays are evident by age 6 months and older and predict later language abilities.[88,89] Difficulties in postural control can appear by age 6 months (eg, delayed sitting) and are persistent.[90]

Differences in object use have been also observed in infants subsequently diagnosed with autism. Although no differences were observed in ability to predict movements of occluded objects,[91] reduced exploratory behaviours were observed in infants aged 10 months.[92] By age 18–24 months, reduced exploratory toy play and unusual toy interests (eg, vacuums, armpits, and specific hats) have been observed.[93]

Repetitive behaviours have been noted by age 9 months, particularly unusual visual inspection of objects (eg, holding and inspecting an object close to the face).[94] By age 12 months, infants later diagnosed with autism displayed more frequent stereotyped motor mannerisms, repetitive object use, and repetitive head movements.[95] Self-injurious behaviours have been observed in infant siblings by age 9 months, although these are not specific to toddlers later diagnosed with autism.[95]

Individual-level predictions based on behavioural characteristics

Screening approaches based on early behavioural signs have used infant surveys based on caregiver report and clinical observation (table). In a cohort of infants for whom there were existing caregiver or professional concerns, the Early Screening for Autism and Communication Disorders questionnaire identified later autism with a sensitivity of 0·86 and a specificity of 0·82.[17] In a study of infant siblings aged 9 months, the Autism Parent Screen for Infants, a caregiver survey, identified infants with later autism with a sensitivity of 0·42 and a specificity of 0·90.[18] Behavioural features derived from the First Year Inventory, a caregiver-reported screening instrument, identified infant siblings aged 12 months and with a later autism diagnosis with a sensitivity of 0·34 and a specificity of 0·91.[19] In a study of infant siblings and low-likelihood infants who were assessed by use of the Autism Observation Scale for Infants, a structured clinical observation, sensitivity values changed from 0·57 at age 6 months to 0·52 at age 12 months and specificity values changed from 0·51 at age 6 months to 0·74 at age 12 months.[20]

Translation of screening tools into clinical practice

Although 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-level predictions of autism.

Notably, most studies to date have focused on infant siblings or those for whom there was an existing professional concern. These populations are 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 (eg, MRI *vs* EEG biomarkers) are difficult because most biomarkers are studied in isolation, and only a few studies have compared or combined different biomarkers at similar ages.[27,30,42] Comparison groups of infants have often been chosen because they have no known factors associated with autism (low-likelihood infants), which likely inflates the accuracy of prediction estimates. Many studies have small sample sizes with little diversity, which makes extrapolation to 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 (eg, ADHD) on prediction accuracy.[52,85] Moreover, most studies have gathered data in academic research labs with a relatively narrow subset of racially, ethnically, and linguistically homogeneous high-income families, whereas fewer studies have been done in those settings within which screening would be expected to occur (eg, studies done in primary clinics or other community settings[43,50,75]). Finally, screening approaches based on machine learning algorithms will require replication based on larger, independent cohorts.

Conclusions and future directions

Research findings to date suggest that a combination of infant measures offers stronger prediction of diagnostic outcomes than a single measure, both within a single

See Online for appendix

Search strategy and selection criteria

We searched MEDLINE via PubMed using broad and expanded search terms including "infant" AND "autism spectrum disorder" AND "prediction" (appendix). For specific sections, additional search terms included "magnetic resonance imaging", OR "health", OR "behaviour". We included articles published in English between Jan 1, 2016, and June 1, 2022, and earlier papers when necessary for context. We also searched the references within the selected papers for relevant articles. We included only prospective longitudinal studies, as well as retrospective studies of medical records, of participants during the infant–toddler period before an established diagnosis of autism by use of criteria of the *Diagnostic and Statistical Manual of Mental Disorders*. The final reference list was compiled on the basis of relevance to the content covered in this Review.

domain (eg, different MRI measures)[96] and from different domains. In a study that combined biomarkers from different domains, prediction of autism was improved when an electrophysiological component was combined with polygenic scores.[27] Studies of digital phenotypes based on computer vision have found that autism prediction improved when multiple behavioural phenotypes (eg, social gaze and speech-gaze coordination) were combined.[43,50] Future studies using machine learning and hybrid statistical approaches based on interpretable components will allow the best weighting of combinations of variables to predict later diagnosis of autism. 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 medical conditions are causal or contributary, and which are consequential, remains a challenge for future research. 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 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 early biomarkers are specific to a later autism outcome. Comparisons of infants at familial risk for autism with those at risk for ADHD are helping to address this issue. One such study reported that responses to the infants' own name did not become a marker specific to autism outcome until age 24 months.[52] Another study reported that, in 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. Increased fearfulness and shyness in infancy were associated with mid-childhood anxiety-related and autism-related behaviours.[97]

A paradox remains that, although several prenatal and perinatal contributory factors have been implicated in autism, behavioural features cohere into a stable diagnosable autism syndrome only after age 18–24 months. However, this extended trajectory gives hope for the identification of intervention domains during infancy and developmental trajectories that could reduce challenges associated with autism. Clinical trials of caregiver-delivered interventions in infant siblings, or after early screening, have been reported with encouraging results.[28,98,99] 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 infants who have a higher likelihood of a diagnosis of autism (eg, infant siblings) but who exhibit no autism-related behavioural signs.[100]

Substantial challenges remain to be addressed before current findings on biomarkers and predictors of infants later diagnosed with autism can be translated into scalable and feasible screening tools that can be used in health systems. Notably, most of the research has been done on infant siblings, a specific subgroup among individuals with autism. A question remains whether many of the infant predictors of later autism identified to date are specific to infants with familial polygenic risk. This question has begun to be investigated with cohorts recruited from the general population with no known genetic risk factor or previous concern,[43,50,75] and in individuals with genetic syndromes, such as fragile-X syndrome, tuberous sclerosis, or neurofibromatosis type 1. For example, in one study of infants with neurofibromatosis type 1, slower neural detection of repeated auditory stimuli was associated with autism-related behaviours at age 14 months.[101]

Addressing the substantial heterogeneity among individuals with autism will be essential for the translation of research on early markers to practical screening approaches. A future research goal is the development of early screening approaches that have been validated on diverse populations in terms of sex, race, ethnicity, and income and that can be used in low-income 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, although the broad goal of linking infant screening to interventions and services that improve quality of life is commendable, future work should consider which safeguards would be needed to mitigate potential risks, such as lack of appreciation of the potential adaptive value of early-emerging autism-related behaviours (eg, self-stimulatory behaviours as a form of adaptive self-regulation) and the use of unnecessary surveillance and

intervention strategies for infants who might not have needed them.

In conclusion, encouraging evidence exists that prediction of later autism in infants is possible. This goal will be accelerated by the advent of new biomarker technologies in the context of large longitudinal studies of infants that simultaneously track the early development of autism at multiple levels of analysis (genetic, brain, health, and behaviour). Key factors for future success include the need for studies to have more diverse populations of infants and frameworks in implementation involving a variety of stakeholders, such as health-care professionals, caregivers, and people with lived experience. These factors will ensure that the screening tools can be effectively used in practice, be linked to beneficial infant and toddler intervention services, and ultimately improve quality of life for individuals diagnosed with autism.

Contributors

GD and MHJ acquired funding and wrote the original draft of the manuscript. ADR was responsible for data curation. All authors conceptualised the Review and contributed to the revision and editing of the manuscript.

Declaration of interests

GD is on the Scientific Advisory Boards of Akili Interactive, Zynerba, Non-verbal Learning Disability Project, and Tris Pharma; is a consultant to Apple, Gerson Lehrman Group, and Guidepoint Global; and receives book royalties from Guilford Press and Springer Nature. GD has developed technology, data, and products that have been licensed to Apple and Cryo-cell. MHJ receives book royalties from Wiley-Blackwell and Oxford University Press. ADR declares no competing interests.

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