

Brain and behavior development in autism from birth through infancy

Mark D. Shen, PhD; Joseph Piven, MD



Introduction

A critical challenge in child psychiatry is the need for the early detection of autism. Although autism spectrum disorder (ASD) affects 1 in 68 children, the average age of diagnosis in the United States is not until 4 years or older.¹ The current diagnostic criteria are hampered by the reliance on behaviorally defined impairments in social interaction and communication, along with the occurrence

Autism spectrum disorder (ASD) is a heterogeneous condition that affects 1 in 68 children. Diagnosis is based on the presence of characteristic behavioral impairments that emerge in the second year of life and thus is not typically made until 3 to 4 years of age. Recent studies of early brain and behavior development have provided important new insights into the nature of this condition. Autism-specific brain imaging features have been identified as early as 6 months of age, and age-specific brain and behavior changes have been demonstrated across the first 2 years of life, highlighting the developmental nature of ASD. New findings demonstrate that early brain imaging in the first year of life holds great promise for presymptomatic prediction of ASD. There is a general understanding in medicine that earlier treatment has better outcomes than later treatment, and in autism, there is an emerging consensus that earlier intervention results in more successful outcomes for the child. Examining early brain and behavior trajectories also has the potential to parse the etiologic heterogeneity in ASD, a well-recognized impediment to developing targeted, mechanistic treatments. This review highlights the current state of the science in the pursuit of early brain and behavioral markers of autism during infancy and examines the potential implications of these findings for treatment of this condition.

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Author affiliations: Carolina Institute for Developmental Disabilities and Department of Psychiatry, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA

Address for correspondence: Mark D. Shen, PhD, Assistant Professor, Carolina Institute for Developmental Disabilities and UNC Department of Psychiatry, University of North Carolina School of Medicine, Campus Box 3367, Chapel Hill, NC, USA 27599-3367 (email: mark_shen@med.unc.edu)

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of restricted interests and repetitive behaviors (*Diagnostic and Statistical Manual of Mental Disorders*, fifth edition [DSM-5]),² which are not readily present in the first 2 years of life. Behavioral symptoms at the first year of life are not specific to ASD,³⁻⁵ and the symptoms that are diagnostic of ASD gradually unfold in the second year of life.⁴⁻⁶ The lack of early behavioral markers is a critical unmet challenge because early detection allows for early intervention, which is effective in decreasing impairments⁷ and results in more positive long-term outcomes for the child.^{8,9}

Given that the diagnostic behavioral features are not present until 2 years of age or later, how do we identify earlier markers of ASD? The solution is the advent of the “infant sibling” study design. This study design leverages the recurrence risk in siblings¹⁰ of about 20%: if an older sibling is already diagnosed with ASD, a subsequent younger sibling has a 15-to-20-fold greater risk of developing the condition than the general population. In addition, 20% to 30% of the remaining younger siblings who do not develop ASD will develop other developmental delays or psychiatric outcomes.¹¹⁻¹³ Infant sibling studies longitudinally follow the younger “high-risk” (HR) siblings starting in infancy until the age when ASD can be reliably diagnosed. Here, we refer to such HR siblings who develop ASD as HR-ASD, and those who do not as HR-negative. In infant sibling studies, HR-ASD infants are compared with HR-negative infants and “low-risk” control infants with no family history of ASD or psychiatric disorders (LR-negative). Behavior assessments are conducted at regular intervals throughout infancy (eg, 6-12-24 months). At least one study, the Infant Brain Imaging Study (IBIS) Network, collects longitudinal magnetic resonance imaging (MRI) throughout the infant interval, whereas other studies collect electroencephalogram (EEG) and other electrophysiological measures. Thus, the infant sibling study paradigm offers an efficient strategy for prospectively studying the earliest behavioral and neural features of autism, before diagnosis. The ultimate goal is to detect early behavioral and biological markers of ASD before behavioral diagnosis is currently possible.

Early behavioral signs

The extant literature of infant sibling studies of autism indicates that diagnostic symptoms, such as social be-

havior, are normal at 6 months of age and unfold and emerge over the first 2 to 3 years of life.⁴ To date, studies of HR infants have not identified differences in the diagnostic symptoms of autism at 6 months in infants who ultimately receive an ASD diagnosis.³⁻⁵ Even symptoms that are exhibited in the first year of life are not specific to autism and thus do not differentiate infants who will develop ASD from those with other developmental delays.¹⁴ By 12 months of age, repetitive behaviors associated with ASD are present in infants who later meet criteria for ASD.¹⁵⁻¹⁷ Thus, symptoms more fully diagnostic of autism appear to develop gradually between 12 and 24 months.⁴⁻⁶

However, differences in other developmental areas have been reported in the first year of life, such as motor skills,^{18,19} visual reception,¹⁸ language,²⁰ and eye gaze patterns of social scenes and faces.²¹⁻²³ Deficits in fine and gross motor skills at 6 months of age in HR-ASD infants¹⁸ suggest that motor development in the first year of life may have a role in the development of autism.^{18,19} Coupled with the presence of increased motor stereotypies in HR-ASD infants at 12 months of age,¹⁵ this points to abnormal development of motor systems between 6 and 12 months of age. In addition, diminished language skills have been reported as early as 12 months of age, followed by atypical receptive-expressive language profiles at 24 months.²⁰

Behavioral signs in the first 2 years of life have been insufficient to accurately predict a later autism diagnosis. At 12 months, parental concerns predicted ASD diagnosis with a positive predictive value (PPV) of 58%.²⁴ At 18 months, behavioral profiles predicted ASD diagnosis with a PPV of 50%.²⁵ Even in a large community sample of toddlers 16 to 23 months old, the Modified Checklist for Autism in Toddlers²⁶—a parent-report questionnaire used as a screening tool for ASD in toddlers—had a PPV of 28%.^{27,28}

Taken together, behavioral research indicates that the defining diagnostic features of autism are not present at 6 months of age, but begin to unfold in the second year of life and consolidate between 18 and 36 months. Although early behavioral markers alone are not sufficiently sensitive or specific to predict later autism diagnosis, the presence of early behavioral differences suggest that the emergence of behavioral features may be preceded by aberrant development of neural features.

Early biological signs

Structural neuroimaging studies of ASD in infancy

One of the most consistent findings from early studies of brain development in ASD has been that head size is normal at birth, but by 2 to 3 years of age, brain size is significantly enlarged. For example, a retrospective head circumference and prospective brain imaging study found indirect evidence that brain enlargement was not present at birth but emerged at the end of the first and second year of life.²⁹ This finding of brain enlargement at 2 to 3 years of age has been confirmed by other studies³⁰⁻³³; however, until recently, there was a dearth of studies directly measuring brain development in the infant period, between birth and toddlerhood. The first direct MRI evidence of brain enlargement in infancy was reported for a sample of 55 infants (10 of whom developed ASD) who were longitudinally imaged between 6 and 24 months of age.³⁴ The HR-ASD group had significantly faster growth trajectories of total brain volume, such that by 12 to 24 months of age, the group had larger brain volumes on average. This was the first study to prospectively measure brain volume during infancy in ASD; however, the sample size was relatively small and thus did not attempt to tease apart individual growth trajectories.³⁴

A significant advance on elucidating the early brain development of ASD was achieved by a recently published study by the IBIS Network.³⁵ In this study, the individual trajectories of 15 HR-ASD infants were followed with three serial MRI scans at 6, 12, and 24 months of age. In addition to measuring total brain volume, this study also decomposed brain volume into precise anatomical measures of cortical surface area and cortical thickness, which both contribute to overall brain volume but are controlled by distinct genetic mechanisms.³⁶ The rationale for decomposing brain volume into surface area and cortical thickness is further underscored by previous evidence in toddlers with ASD that showed that increased brain volume was associated with an increase in cortical surface area but not cortical thickness,²⁹ a finding that was confirmed in a separate sample.³⁷

The IBIS study³⁵ reported that HR-ASD infants had an increased rate of surface area expansion from 6 to 12 months, followed by an increased growth rate

of total brain volume from 12 to 24 months, in comparison with both the HR-negative and LR groups. No group differences in cortical thickness were observed across the 6- to 24-month interval. In addition, there were specific brain-behavior relationships with temporal specificity: higher growth rates of brain volume between 12 and 24 months (but not between 6 and 12 months) were associated with greater autism severity scores in the social domain at 24 months (but not in the repetitive behavior domain). By virtue of following each infant longitudinally, and generating precise measures of cortical surface area, this study was able to generate a machine-learning algorithm that relied primarily on measures of cortical surface area growth between 6 and 12 months of age to predict *on an individual basis* an ASD diagnosis at 24 months. This algorithm correctly predicted subsequent ASD diagnosis with a sensitivity of 88%, specificity of 95%, and PPV of 81%. The findings of this study emphasized the importance of moving beyond group-level differences toward individual-level prediction and indicated that brain differences are present at 6 to 12 months of age, before the onset of the defining behavioral features of autism described above.

Two recent studies have detected another brain anomaly in the first year of life in infants who are subsequently diagnosed with ASD. In the first study,³⁴ infants who later developed ASD (HR-ASD; $n=10$) had an excessive amount of cerebrospinal fluid (CSF) in the subarachnoid space surrounding the cortical surface of the brain (ie, “extra-axial CSF”). The amount of extra-axial CSF (EA-CSF) at 6 months of age preceded the onset of autistic symptoms and was predictive of both their later autism diagnosis and severity of autism symptoms at 3 years of age. These findings were recently replicated in a larger, independent cohort of infants in the IBIS Network ($N=343$, of which $n=47$ were HR-ASD).³⁸ In this second study, infants who later developed ASD had 18% more EA-CSF at 6 months than the control groups (HR-negative and LR groups). EA-CSF volume remained persistently elevated through 24 months of age, relative to controls. Infants in who were later diagnosed with the most severe autism symptoms had a more pronounced increase of EA-CSF—nearly 25% greater EA-CSF at 6 months than the controls.³⁸ In addition, excessive EA-CSF at 6 months was associated with early motor deficits in the first year of life, suggesting that increased EA-CSF may affect motor develop-

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ment during the prodromal period in autism, before behavioral diagnostic signs of ASD typically arise. Finally, a fully cross-validated machine-learning algorithm relying on the amount of EA-CSF at 6 months predicted later ASD diagnosis at 24 months with 66% sensitivity and 68% specificity.³⁸ This prediction algorithm was then externally validated in the 2013 sample³⁴ (in order to test the algorithm on an independent data set), which yielded 80% sensitivity and 67% specificity in predicting an ASD diagnosis at 24 months on the basis of EA-CSF volume at 6 months.³⁸ Thus, although these prediction metrics are not yet strong enough to be clinically useful as a *single stand-alone marker* to predict individual outcomes, the replication and reliability of the findings between the two independent data sets^{34,38} indicates that increased EA-CSF at 6 months could be a potential early stratification marker of a biologically based, etiologically homogenous subtype of ASD.

Taken together, these studies show that HR-ASD infants have elevated levels of EA-CSF at 6 months,^{34,38} increased growth rate of the cortical surface between 6 and 12 months,³⁵ and total brain volume overgrowth between 12 and 24 months of age.³⁵ Thus, brain changes are present during the prodromal period in ASD before diagnosis and precede (or coincide with) behavioral differences. At 6 months of age, brain size is normal, but there is an excessive amount of EA-CSF.^{34,38} This is a time when the first behavioral alterations start becoming detectable, including motor delays.^{5,18,28} Indeed, excessive EA-CSF at 6 months was found to be associated with early motor deficits at 6 months.³⁸ Between 6 and 12 months of age, there is rapid expansion of cortical surface area,³⁵ which is concurrent with the onset of sensory and attention problems, such as deficits in visual reception¹⁸ and orienting to salient social cues in the environment.³⁹ Interestingly, hyperexpansion of surface area between 6 and 12 months was observed in cortical areas associated with sensorimotor processing.³⁵ Between 12 and 24 months, there is an increased growth rate of total brain volume,^{34,35} which is concurrent with the emergence of social deficits.⁴ Indeed, the rate of brain volume growth between 12 and 24 months was associated with autism-specific social deficits.³⁵ Thus, early changes in brain development coincide with the age when early sensorimotor and visual orienting differences emerge, which may have downstream effects on later social development and the consolidation of behaviors that are diagnostic of ASD.

How might increased EA-CSF in infancy and early brain overgrowth be related? Is it possible that accumulation of stagnant CSF over the surface of the brain influences cortical brain development? CSF has many important functions, including the removal of potentially harmful byproducts of brain metabolism, such as β -amyloid and tau.^{40,41} Stagnation of CSF leads to the accumulation of waste byproducts and neuromodulators in brain tissue that may alter the extracellular environment of neurons and impact their function.^{42,43} CSF also serves as a means of transporting important cytokines, growth factors, and other signaling molecules, such as insulin-like growth factor (IGF1 and IGF2), which are required for the normal development of the neocortex.^{40,44-46} An imbalance of CSF production and absorption alters the concentration of these factors and could lead to serious consequences on cortical development.⁴⁷ For example, stagnation of CSF flow in animal models leads to an alteration of neurogenesis and premature migration of progenitor cells.⁴⁷ Indeed, there is evidence that the composition of CSF drawn from the subarachnoid space in infants with increased EA-CSF has a higher protein concentration than CSF drawn from the ventricles or spinal column,⁴⁸ and CSF in normal infants.⁴⁹ Of course, in the context of a research study, it would be too invasive to draw CSF from the brain in children with ASD. Future studies are needed to test the hypothesis that stagnant or elevated EA-CSF has a different composition of trophic growth factors (IGF1, IGF2) and neuroinflammatory proteins (β -amyloid, tau).^{40,44-46}

White matter brain connectivity

On the basis of diffusion tensor imaging (DTI) tractography, HR-ASD infants have been reported to have abnormalities in white matter (WM) organizational structure as early as 6 months of age in multiple fiber tracts across the brain.^{50,51} Aberrant WM integrity has been observed by 6 months in the genu of the corpus callosum,⁵¹ and WM integrity in the genu and cerebellar peduncles is significantly associated with abnormal sensory responsiveness at 24 months, a clinical domain particularly affected in individuals with ASD.⁵² These reports of reduced WM organization in HR-AD infants are consistent with studies of toddlers with ASD.^{53,54}

Functional brain differences in infancy

Functional connectivity MRI (fcMRI) is another type of MRI scan that can be acquired in infants during natural sleep to characterize functional brain connectivity. In a prospective study of 59 HR infants, a recent IBIS study found that fcMRI at 6 months could accurately identify which infants would receive an ASD diagnosis at 24 months.⁵⁵ First, functional connections at 6 months were identified on the basis of their association with ASD-related behaviors at 24 months (ie, scores on social behavior, language, motor development, and repetitive behavior). Then, a machine-learning prediction algorithm was conducted on these functional connections, utilizing a fully cross-validated scheme (ie, subjects who were tested in the “leave-N-out” folds of the classifier were then left out of the feature identification and reduction procedures to avoid contaminating the testing with the training information). The prediction algorithm using fcMRI data from 6-month-olds achieved 100% PPV, 82% sensitivity (correctly predicting 9 of the 11 infants who received an ASD diagnosis at 24 months), and 100% specificity (correctly predicting 48 of 48 infants who were negative for ASD at 24 months of age).⁵⁵ This study provided the first evidence that *functional neuroimaging* in 6-month-old infants could accurately predict which individuals would receive a diagnosis of ASD at 24 months of age.

These recent fcMRI results, coupled with electrophysiological evidence for differences in EEG and event-related potential (ERP) response,^{56,57} add to the increasing evidence that there are alterations in both brain function and brain structure (as described above) that are present in the first year of life in infants who later received an ASD diagnosis.

Conclusions and future directions

Infant sibling studies have shown that ASD-specific behaviors emerge in the latter part of the first and during the second year of life,⁴ with diagnosis typically occurring around 4 years of age.¹ Before 12 months of age, behavioral differences between those who develop ASD vs those who do not, have only been identified at the group-average level (eg, see Estes et al¹⁸). Behavioral markers in the first year of life have not been shown to be sensitive or specific enough at the individual level for clinically useful prediction of later ASD diagnosis.

Thus, it is current practice in child psychiatry to not initiate treatment until after behavioral diagnosis of ASD. However, there are recent data that indicate that earlier behavioral intervention for autism is more effective than later treatment.⁵⁸⁻⁶¹ Thus, there is a need for both early and biologically derived markers for ASD in infancy to reliably detect which children need treatment, what type of treatment, and when to initiate treatment.

The potential for an early biological marker for ASD

The promise of a biological marker for ASD is a lofty and elusive goal, and the benchmarks for success are justifiably high. The US National Institutes of Health (NIH) working group established the definition of a biological marker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention” (NIH Biomarkers Definitions Working Group,⁶² 2001). Biological markers should have valuable applications, which may include the following (see ref 62, p 91):

- “Use as a diagnostic tool for the identification of those patients with a disease or abnormal condition”
- “Use as a tool for staging of disease...or classification of the extent of disease”
- “Use as an indicator of disease prognosis”
- “Use for prediction and monitoring of clinical response to an intervention.”

We have made considerable progress in pursuing these benchmarks for autism, particularly in the following areas (see *Figure 1*):

- *Early markers to predict ASD.* The first year of life is a period of tremendous neural plasticity, as the brain doubles in size from birth to 1 year.⁶³ Thus, it is not surprising that intervention during this time has been shown to produce better outcomes for children with ASD. This underscores the critical need for early predictive markers for early detection of autism. In the last year alone, two studies have shown predictive accuracy (PPV over 80%) that holds promise for early prediction of autism.^{35,55}
- *Age-specific treatment windows.* Longitudinal studies of infants who develop autism have identified specific brain changes during specific time periods (eg, cortical surface area expansion from 6 to 12 months³⁵), which may point to specific windows of

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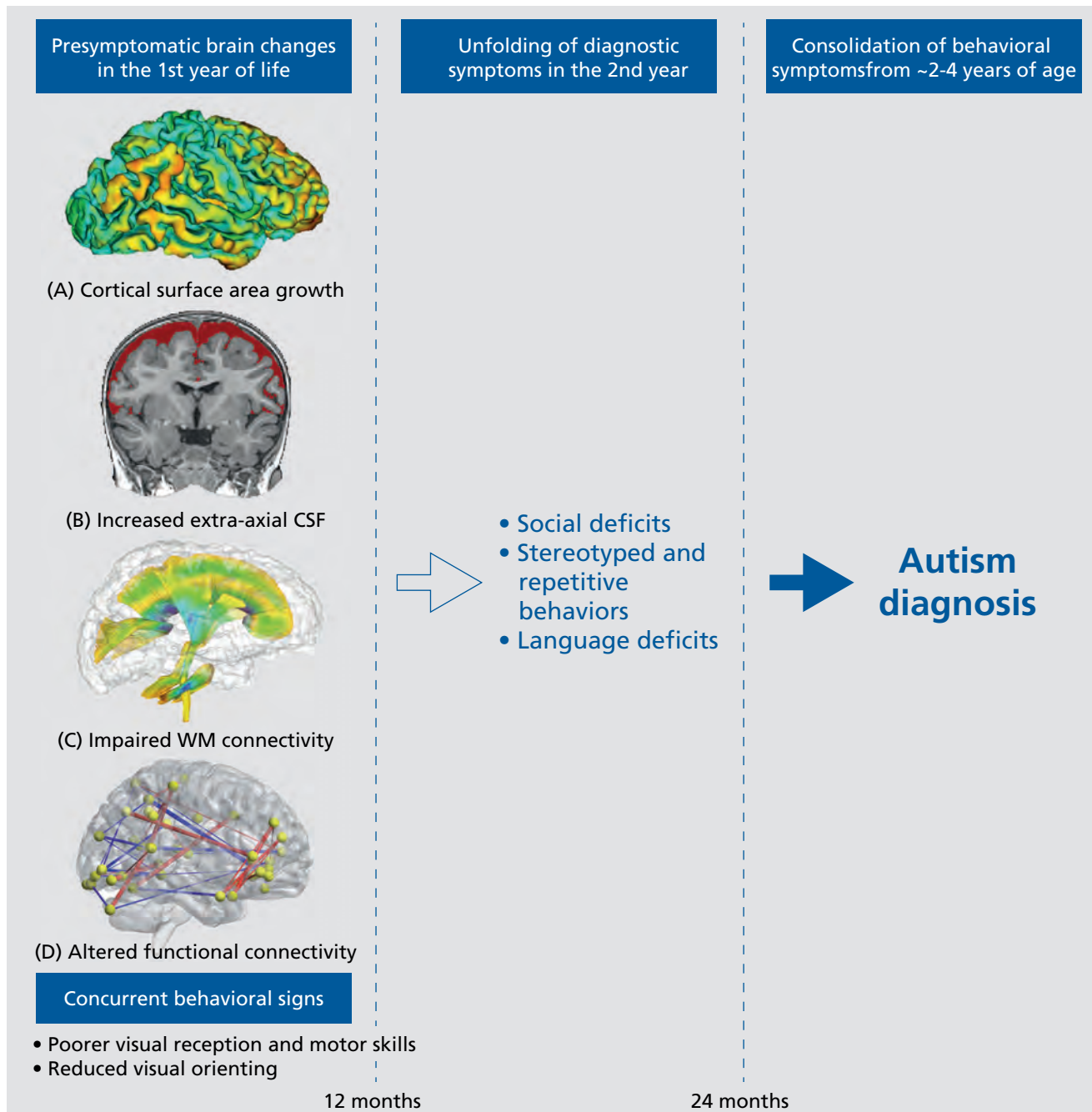


Figure 1. Several brain features have been identified during the presymptomatic period in autism—before the unfolding of the diagnostic symptoms of autism. (A) Cortical surface area growth between 6 and 12 months of age is predictive of an eventual autism diagnosis³⁵; (B) Increased volume of extra-axial CSF at 6 months of age (ie, CSF in the subarachnoid space; colored in red) is associated with autism diagnosis, early motor deficits, and later autism severity^{34,38}; (C) Aberrant white matter connectivity (fractional anisotropy in the genu of the corpus callosum) is present at 6 months of age and is predictive of the severity of repetitive behaviors and sensory responsiveness at the time of diagnosis⁵⁰⁻⁵²; (D) Altered functional connectivity at 6 months of age predicts an eventual autism diagnosis.⁵⁵ These neural features are concurrent with early behavioral signs in the first year of life, followed by the unfolding of diagnostic symptoms in the second year of life, and the consolidation of behavioral symptoms that are fully diagnostic of autism. CSF, cerebrospinal fluid; WM, white matter.

opportunity for treatment when the brain is most plastic and malleable to treatment.

- *Stratification markers to address heterogeneity.* There is tremendous phenotypic heterogeneity in ASD, which has hampered efforts toward targeted treatments. Parsing the heterogeneity in ASD and identifying biological subtypes have become major initiatives in child psychiatry, as evidenced by the strategic objectives of the US National Institute of Mental Health.⁶⁴ Thus, there is a need for stratification biomarkers that can separate children into subtypes that share a common pathophysiology (eg, increased EA-CSF^{34,38}). Such stratification biomarkers have the potential to carve up the etiological heterogeneity and map on to specific, mechanistically targeted treatments.

Clinical and ethical implications of early detection

The potential for presymptomatic detection of ASD in infancy has important clinical, ethical, and social implications that warrant consideration. First, it is unlikely that neuroimaging in infancy will replace expert clinical diagnosis, but rather that objective quantifiable biological markers (eg, measures generated from infant brain scans) may serve as an additional screening tool for clinicians to flag infants at very high risk for developing autism.

Second, although the studies reviewed herein have shown that it is possible for brain features at 6 to 12 months of age to predict ASD diagnosis at 24 months, there is ample research demonstrating that some ASD children will not fully manifest the diagnostic features of ASD until later in childhood.⁶⁵⁻⁶⁷ Thus, the studies to date on early prediction of autism have not attempted to detect *all* children who might later receive a diagnosis of autism, but those who receive an autism diagnosis at the typical age of diagnosis. For this reason, the focus of early prediction should be on *positive* predictive value (PPV: the probability that a *positive* test will identify children with a *high likelihood* of developing the disorder) and not on *negative* predictive value (NPV: the probability that a *negative* test will rule out children with a *low likelihood* of developing the disorder). In other words, an early predictor with high PPV could

appropriately flag a child who is likely to develop ASD, and then route them to early treatment; whereas an early predictor with high NPV could not confidently rule out the possibility that the child will eventually develop ASD later in childhood, because a negative test in this case would inappropriately give parents a false sense of security.

Lastly, careful consideration must be devoted to the parental and societal effects of a positive predictive result. Studies of predictive testing and early detection in other conditions have suggested there are potential benefits to families and society. For example, predictive testing or presymptomatic screening has been shown to improve family coping.⁶⁸ Furthermore, most studies of predictive genetic testing show limited or no adverse psychological impact after a positive result.⁶⁹⁻⁷² Similarly, most studies of newborn screening report minimal psychological distress for parents after early diagnosis.^{68,73,74} However, there are still concerns about the psychological impact on parents who receive results from pediatric predictive testing,⁷⁵ and additional research should be focused on identifying and assisting those parents who may be more vulnerable to adverse outcomes after receiving results.^{74,76} Furthermore, additional research and supports need to address the challenge of managing the child's condition,⁷³ impact on family dynamics,⁷⁷ potential for discrimination and stigma,⁷⁸ and ever-changing societal perceptions.⁷⁹

Although considerable work lies ahead of the autism field, the development and validation of biomarkers for ASD will help move the field of psychiatry toward its aspiration of precision medicine,⁸⁰ in order to determine the best treatment, at the optimal time, for specific subtypes. The goal might be to combine biomarkers with existing clinical expertise in behavioral assessments to detect autism earlier and more reliably, with the goal to improve the long-term outcomes for children affected by autism. □

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Desarrollo conductual y cerebral en el autismo entre el nacimiento y la infancia

El trastorno del espectro autista (TEA) es una condición heterogénea que afecta a uno entre 68 niños. El diagnóstico está basado en la presencia de alteraciones conductuales características que aparecen durante el segundo año de vida y que no son totalmente típicas hasta los tres o cuatro años. Estudios recientes sobre el desarrollo precoz, tanto cerebral como conductual, han aportado novedosos conocimientos respecto a la naturaleza de este cuadro. En los estudios de imágenes, ya a los seis meses de edad se han identificado características que son específicas para el autismo; también se han observado cambios conductuales y cerebrales específicos para la edad durante los dos primeros años de vida, lo que resalta la naturaleza evolutiva del TEA. Hay nuevos hallazgos que demuestran que imágenes cerebrales precoces durante el primer año de vida constituyen una gran promesa para la predicción del TEA previo a la aparición de los síntomas. En medicina existe el concepto que un tratamiento más precoz tiene mejor resultado que uno más tardío, y en el autismo ha surgido el consenso que una intervención más precoz obtiene resultados más exitosos para el niño. La evaluación de las manifestaciones conductuales y cerebrales precoces también tiene el potencial de analizar la heterogeneidad etiológica del TEA, la cual constituye un impedimento bien reconocido para el desarrollo de tratamientos específicos. Esta revisión destaca el estado actual de la ciencia en cuanto a la búsqueda de marcadores conductuales y cerebrales precoces de autismo durante la infancia y analiza las potenciales implicancias de estos hallazgos en el tratamiento de esta patología.

Développement du cerveau et du comportement dans l'autisme de la naissance à la petite enfance

Le trouble du spectre de l'autisme (TSA) est une maladie hétérogène qui touche 1 enfant sur 68. Le diagnostic, rarement posé avant 3 ou 4 ans, est basé sur la présence de déficits comportementaux caractéristiques, apparaissant lors de la deuxième année de vie. De récentes études sur le développement précoce du cerveau et du comportement ont éclairé différemment la nature de cette maladie. Une imagerie cérébrale spécifique de l'autisme est identifiée dès l'âge de 6 mois et les modifications du cerveau et du comportement liées à l'âge mises en évidence lors des 2 premières années de vie, soulignent la nature développementale du TSA. D'après des données récentes, l'imagerie cérébrale précoce dans la 1^{re} année de vie est très prometteuse en termes de prédiction présymptomatique du TSA. En médecine, il est généralement admis qu'un traitement précoce donne de meilleurs résultats qu'un traitement tardif et dans l'autisme, le consensus actuel est qu'il est bénéfique pour l'enfant d'intervenir tôt. L'examen des trajectoires précoces du cerveau et du comportement permet d'analyser l'hétérogénéité étiologique du TSA, frein bien connu au développement de traitements mécanistiques ciblés. Cet article met en lumière l'état actuel de la science dans la recherche de marqueurs précoces cérébraux et comportementaux de l'autisme pendant l'enfance et il analyse les implications potentielles de ces résultats pour le traitement de cette maladie.