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A Developmental Neuroscience Approach to the Search for Biomarkers in Autism Spectrum Disorder

Kandice J. Varcin, PhD[1] and **Charles A. Nelson III, PhD**[1,2]

[1]Laboratories of Cognitive Neuroscience, Division of Developmental Medicine, Boston Children's Hospital, Harvard Medical School, Boston MA USA

[2]Graduate School of Education, Harvard University, Cambridge MA USA

Abstract

Purpose of review—The delineation of biomarkers in autism spectrum disorder (ASD) offers a promising approach to inform precision-medicine based approaches to ASD diagnosis and treatment and to move toward a mechanistic description of the disorder. However, biomarkers with sufficient sensitivity or specificity for clinical application in ASD are yet to be realized. Here, we review recent evidence for early, low-level alterations in brain and behavior development that may offer promising avenues for biomarker development in ASD.

Recent findings—Accumulating evidence suggests that signs associated with ASD may unfold in a manner that maps onto the hierarchical organization of brain development. Genetic and neuroimaging evidence points towards perturbations in brain development early in life, and emerging evidence indicates that sensorimotor development may be amongst the earliest emerging signs associated with ASD, preceding social and cognitive impairment.

Summary—The search for biomarkers of risk, prediction and stratification in ASD may be advanced through a developmental neuroscience approach that looks outside of the core signs of ASD and considers the bottom-up nature of brain development alongside the dynamic nature of development over time. We provide examples of assays that could be incorporated in studies to target low-level circuits.

Keywords

biomarkers; autism spectrum disorder; neurodevelopmental; early development

Introduction

Neurodevelopmental disorders include conditions that typically emerge during early development, such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder. These disorders impact development in a wide-range of functional domains, including social, cognitive and language domains. Despite obvious neural underpinnings,

Corresponding author: Charles A. Nelson III, PhD, Laboratory of Cognitive Neuroscience, 1 Autumn Street, 6th Floor, Boston, MA 02215; Phone: +1 617-355-0401; charles_nelson@harvard.edu.

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these heterogeneous disorders are currently behaviorally defined. The delineation of biological markers (i.e., “biomarkers”) that signal risk, predict outcome and can monitor treatment response offer a promising approach towards establishing biological and mechanistic-based descriptions of neurodevelopmental disorders, as well as allowing for precision-medicine approaches to treatment. Here we focus on ASD to elucidate (1) the rationale for the search for biomarkers in the context of this complex neurodevelopmental disorder, (2) the promise of brain-based markers of risk and prediction, and (3) how biomarker development could be advanced through a developmental neuroscience lens that looks outside of the core, diagnostic signs of ASD and considers the hierarchical and integrative nature of brain development alongside the dynamic nature of early development across time.

The Utility of Biomarkers in Autism Spectrum Disorder

ASD refers to a neurodevelopmental syndrome characterized by impairment in social communication and the presence of restricted and repetitive behaviors [1]. Current estimates suggest that 1–2 people in every 100 meet criteria for ASD [2] with a higher prevalence rate amongst males compared to females [3] (at least in non-syndromic presentations). Amongst individuals with ASD, there is significant phenotypic heterogeneity in cognitive and language abilities and adaptive function alongside variability in the presence of co-occurring medical conditions, such as epilepsy and gastrointestinal problems.

Recent research into the etiological bases of ASD suggests that risk is conferred through both genetic and environmental factors, laying the foundation for a multifaceted and dynamic profile of ASD susceptibility [4*]. Significant advances in gene discovery have unveiled a complex genetic architecture in ASD risk that involves hundreds of biologically pleiotropic genes, leading to the conceptualization of ASD as a syndrome that encompasses hundreds of rare disorders [5*]. It is becoming increasingly apparent that there are multitudes of pathways to ASD, many of which are yet to be delineated.

This heterogeneity through all levels of examination in ASD (from cellular through to behavioral) poses challenges for diagnosis, prognosis, stratification, identifying treatment targets, treatment selection, treatment response monitoring and in the delineation of key pathological mechanisms. Herein lies the promise and potential of biomarkers in ASD - that is, providing a means by which to dissect the heterogeneity amongst individuals with ASD through the identification of more biologically homogenous subgroups in order to aid early detection, predict outcomes and inform more precise, biologically-based, intervention targets [6].

A generally accepted definition of a biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention” [7]. Davis et al. [8**] recently proposed a working taxonomy of biomarkers for neuropsychiatric disorders that aims to foster greater precision and consistency in the use of the term ‘biomarker’ in relation to neurodevelopmental disorders. This taxonomy groups biomarkers into categories of (1) risk, (2) diagnosis or trait, (3) state or acuity, (4) stage, (5) treatment response and (6) prognosis.

Embedded within this taxonomy is the notion of different functional classes of biomarkers that serve different purposes; it is neither assumed nor precluded that a single biomarker will function across multiple classes.

In ASD, biomarkers with sufficient sensitivity and specificity to have clinical applicability, in any of the functional classes, are yet to be realized. However, intensive research efforts are currently underway, particularly in the delineation of biomarkers of risk (i.e., that can identify children at risk for ASD prior to the emergence of overt signs), diagnosis (i.e., that are sensitive and specific to ASD for clinical stratification purposes) and treatment response monitoring (i.e., to establish treatment effectiveness). The overarching goal of this work is to allow for a precision-medicine based approach to ASD diagnosis and treatment.

Advancing our Understanding of ASD through a Brain-Based Approach

The investigation of the developing brain is a particularly promising route for biomarker (and mechanistic) discovery in ASD. A number of recent reviews have highlighted the vast array of brain-based markers under investigation [9–12]. Examining brain-based markers in ASD has intuitive appeal considering ASD is conceptualized as a *neuro*developmental disorder [1]. Further, emerging evidence suggests that despite significant genetic (and clinical) heterogeneity, many of the genes implicated in ASD converge on common biological pathways, particularly those involved in neuronal activity, transcriptional regulation, synaptic function and structure and excitatory and inhibitory neurotransmission [13*, 14*]. This convergence highlights a means by which hundreds of genetic variants may produce a common phenotype (i.e., an equifinality) – that is, by leading to perturbations in neural development. In this context, brain-based signatures may exist across sub-groups of individuals with ASD.

Brain-based measures offer an especially promising approach towards the development of biomarkers of risk and prediction, especially in light of emerging evidence suggesting that alterations in brain development can be traced to early fetal development [14*]. Prospective studies of infant siblings of children with an ASD diagnosis (who are at almost 20 times increased risk of being diagnosed with ASD compared to the general population [15]) have demonstrated that the behavioral features that define ASD (i.e., social communication deficits and restricted and repetitive behaviors) do not typically manifest until the end of the first year of life or across the second year [16]. However, in this same population of infants, abnormalities in brain function [17, 18] and structure [21] have been identified within the first year. In other words, changes in the brain appear to precede changes in behavior and the manifestation of overt behavioral signs of ASD.

The hierarchical and integrative nature of brain development: looking outside the core signs of ASD

The brain is built in a hierarchical manner whereby the neuronal circuits that underlie sensory and motor systems are established first in early postnatal life followed by circuits that sub-serve ‘high-level’ functions such as language, cognition and social skills [20–23]. This hierarchical development leads to an integrative system in which high-level circuits

incorporate and depend on the quality of information provided by basic or 'low-level' circuitry [20]. The refinement of neuronal circuits occurs, predominately, during critical periods in early development [24], generally within the first postnatal years. This bottom-up nature of brain development implies that perturbations in basic sensory and motor circuitry (which may stem from a dysfunction in GABAergic signaling that alters the excitatory and inhibitory balance during periods of circuit refinement; [25]) could exert cascading effects on higher-level, integrative brain functions [20, 23, 25]. In support of this account, recent evidence indicates that many of the genes implicated in ASD risk are also implicated in synaptic plasticity and neuronal differentiation [26], suggesting circuit refinement, at both low- and high-levels, may be perturbed in ASD [25, 27–28]. While we are yet to identify specific circuits impacted in humans with ASD, there is increasing evidence, especially from animal models, that cerebellar circuitry (e.g., cerebello-thalamo-cortical loops) may be disrupted [28]; while these loops support motor functions, they also encompass projections to regions involved in higher-level cognitive processes in humans, such as the frontal and prefrontal regions [29].

Although the majority of research in ASD has focused on higher-level social communicative and cognitive deficits, there is emerging evidence for alterations in more basic sensory and motor processing in individuals with ASD [30–33]. Indeed, a meta-analysis of ASD studies reported that motor disturbances are widespread, large and occur in the majority of individuals with ASD [34]. Deficits have been found in gross and fine motor skills extending through to oculomotor disturbances [33–35]. Atypicalities in sensorimotor development in infancy have been reported to be amongst the earliest emerging behavioral signs associated with ASD [36, 37**, 38*]. And, recently, high rates of parkinsonism have been reported amongst adults with ASD, further implicating dysfunction within the motor system and possibly, dopaminergic pathways [39*].

Beyond the prevalence of sensorimotor disturbances, atypicalities in this domain have been linked to ASD outcome and severity. Flanagan et al. [40] found that motor coordination deficits at 6 months (marked by head lag when pulled to sit) were associated with a later diagnosis of ASD. In a prospective study of infants at high-risk for ASD, Estes et al. [37**] found that atypical sensorimotor development at 6 months of age was predictive of ASD outcome at 24 months of age in those infants most severely affected. Further, motor impairments appear to manifest prior to deficits in higher-level cognitive and social communicative skills, speaking to the primacy of this system in ASD [37**, 41–42]. Consistent with the integrative and hierarchical nature of brain and behavior development, early motor development in ASD has been associated with later expressive language abilities [36] and social skills development [43–44].

Converging with findings of sensorimotor disturbances at the behavioral level is evidence from brain-based measures demonstrating alterations in the processing of non-social sensory stimuli in the visual, auditory and somatosensory domains in ASD [31,45–46*]. Altered information processing in visual and auditory pathways (which can be indexed via visual and auditory evoked potentials) has been reported in individuals with non-syndromic ASD [12, 46*–47] and Fragile X syndrome and TSC (the most commonly occurring monogenic disorders associated with ASD; [48–49]). Perturbations in cerebellar circuitry and function

(which undergoes rapid growth in postnatal development) have been purported to account for early-emerging sensorimotor deficits in ASD [50*]. Using an eyeblink conditioning paradigm (a non-invasive assay of cerebellar circuits), Kloth et al. [51] identified alterations in eyeblink conditioning across five mouse models of ASD, with the nature of the alteration varying as a function of genetic model. Eyeblink conditioning in human studies of ASD are scarce. However, in the two studies (to the best of our knowledge) that have used this paradigm, deficits in eyeblink conditioning were identified in individuals with ASD, suggestive of abnormal cerebellar function in this group [52–53].

In summary, there is genetic, behavioral and brain-based evidence that points toward alterations in circuitry underlying basic sensory and motor processes in ASD. Currently, primary sensory processes and motor development remain understudied domains in ASD. Brain-based assays of these low-level processes in early development in populations at risk are particularly lacking. From a biomarker development standpoint, low-level sensory and motor pathways can be assayed non-invasively from very early in life. For example, scalp-recorded visual evoked potentials [VEPs] and auditory evoked potentials [AEPs] can be used to interrogate basic visual and auditory pathways starting in early infancy. Eyeblink conditioning is a cerebellar-dependent task that has been used with children from early infancy and in children with developmental disorders [54]. These low-level circuit assays (e.g., VEP, AEP and eyeblink conditioning) can be used irrespective of age, language and cognitive level, making them particularly amenable for use with infants and populations with developmental delays. In addition, assays of more basic circuitry hold high translational potential as the same measures have been used in humans and animal models of ASD [e.g., 51, 55*] and, in some cases (such as VEPs), are currently used in clinical settings. Establishing the specificity of these low-level impairments to ASD will be an important future avenue of research.

Mapping developmental trajectories: a temporal dimension to the search for biomarkers

Emerging evidence from genetic research, postmortem studies and animal models of ASD suggest that perturbations in brain development in ASD may have their onset during prenatal development and/or early postnatal life [14*, 56]. As previously outlined, there is evidence that alterations in brain development in ASD converge at the level of synapse formation and function and may contribute to alterations in excitatory and inhibitory neurotransmission and circuit development in ASD [14*, 25]. Therefore, brain-based measures that can be used from early infancy and that index purported mechanisms underlying ASD (such as alterations in neural connectivity, circuit development and excitation and inhibition imbalance) hold significant potential in biomarker discovery in ASD; electroencephalography (EEG) is one such measure [10].

EEG provides a temporally precise index of postsynaptic activity of large populations of synchronous neurons that are mediated by excitation and inhibition interactions [57]. Using EEG, investigators have demonstrated the sensitivity of this technique to developmental change early in life in typical development and in infants at high-risk for ASD [58–60]. Bosl

[59] used EEG to measure multiscale entropy, (a measure of physiological complexity that contains information about neural network dynamics) in infants at high- versus low-risk for ASD from 6 to 24 months. Differences in trajectories of multiscale entropy between 9 to 12 months differentiated infant siblings at high- and low-risk for ASD, capturing a transitory, albeit, potentially informative shift in development associated with ASD risk. Also using EEG, Tierney et al. [60] found that developmental trajectories of resting EEG power (which indexes neural oscillations mediated by excitation and inhibition interactions) from 6 to 24 months distinguished infants at high- versus low-risk familial risk for ASD. Attesting to the idea that EEG indexes mechanisms purported to underlie ASD (such as alterations in neuronal connectivity and excitation and inhibition imbalance), numerous studies have found alterations in EEG activity in ASD [61]. However, Bosl [59] and Tierney's [60] findings also highlight how above and beyond a single time point, there is considerable information embedded in developmental *trajectories* across early infancy. This point has also been demonstrated using other brain imaging techniques, such as magnetic resonance imaging (MRI). For example, Wolff et al. [19] found that infants at high familial risk who met criteria for ASD had different trajectories of anatomical connectivity between 6 and 24 months compared to infants at high-risk who did not meet criteria for ASD.

There are a number of reasons for why examining brain development over time is a promising route for the development of biomarkers of risk, prediction and stratification. Namely, the hierarchical nature of brain development implies that early perturbations during basic circuit refinement may lead to widespread alterations while later-occurring impacts to the brain may contribute to more specific and localized disruptions [23]. Within this context, the heterogeneity in phenotype and severity in ASD may be partly explained by *when* in development pathophysiological mechanisms (i.e., genetic, environmental and/or their interplay) exert an influence on the brain. Therefore, rather than a common point in development in which the brain is impacted across individuals, the temporal emergence of neural abnormalities (and the type of alteration to brain development) may differ amongst subgroups of individuals with ASD, contributing to differences in phenotypic expression. As circuitry supporting higher-level social and cognitive functions is refined at later developmental stages, as compared to circuitry supporting primary motor and sensory processes, there is more 'time' for development in these higher domains to be perturbed. Moreover, higher-level functions are the end product of a developmental cascade of lower-level 'building blocks', thus, they could be impacted by alterations in lower-level sensory functions or independently impacted by a later 'hit'. By this account, capturing when in development, and in what domains (i.e., low- versus higher-level), individuals deviate from a typical trajectory, may prove to be important in the stratification of more homogenous sub-groups of individuals with ASD. Herein, prospective, longitudinal studies are a critical tool in the armamentarium of biomarker development.

Further, while core ASD-signs and associated behaviors appear to unfold across early development, these signs are dynamic and show change across time. From a biomarker standpoint, within such a dynamic system, it cannot necessarily be assumed that a marker, identified at a particular point in development, will hold the same sensitivity and specificity across time. Similarly, it cannot be assumed that the presence or absence of a particular behavior or biological marker at a single, cross-sectional developmental stage will be static

across time. Longitudinal examinations enable this dynamism to be harnessed in order to explore characteristics embedded within developmental trajectories that may signal risk, predict outcome or inform mechanisms underlying phenotypic variability in ASD.

An important consideration in the study of early developmental trajectories as a means to advance biomarker development is in the selection of a comparison, or control, sample. The majority of research to date has compared early developmental trajectories amongst high-risk infants to typically developing infants. Comparisons to typical development are valuable, particularly if we consider ASD a deviation from a typical developmental trajectory. Comparisons to typically developing infants can provide insight into when in development infants with or at high-risk for ASD deviate from a typical developmental trajectory, and the degree of deviation that is required to lead to functional disturbances or symptom manifestation. However, comparisons beyond typical development, to other neurodevelopmental disorders (e.g., intellectual disability, ADHD) are critical to establish the specificity of early markers to ASD. For many brain-based biomarkers currently under investigation in ASD (e.g., EEG-based measures of connectivity, complexity and low-level circuit assays), we are yet to characterize their developmental maturation in typical development. Hence, characterizations of these neural processes and how they relate to developmental outcomes in typical development should be a focus of future work, alongside ASD biomarker discovery.

Conclusion

The search for brain-based biomarkers in ASD sits amongst an array of investigations into genetic, biochemical, immune, epigenetic, and metabolic biomarkers in ASD [9]. The heterogeneity inherent to ASD necessitates such a broad approach. It is likely the case that sets of markers, rather than a single marker, will be required to yield biomarkers with sufficient sensitivity and specificity for clinical application. In concurrence with a number of other investigators [e.g., 25, 32], we suggest that by looking beyond the core domains of ASD and into the lower-level ‘building blocks’ that underlie higher-level social and cognitive development we may be able to move the field towards neurobiological and mechanistic-based characterizations of ASD that will serve to complement current behavior-based descriptions.

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Key points

- The delineation of biomarkers in ASD is a promising approach towards precision-based advances in diagnosis and treatment.
- Biomarkers with sufficient sensitivity and specificity for clinical application are yet to be identified in ASD.
- Alterations in brain development manifest early in life in ASD, prior to the emergence of core behavioral signs, highlighting a promising route for the development of biomarkers of risk and prediction.
- Alterations in motor and sensory processes may be amongst the earliest signs associated with later ASD.
- Brain-based assays of low-level sensory and motor circuits across early development offer a promising avenue for future research in ASD biomarker development.