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Review

Early identification of autism spectrum disorders

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HIGHLIGHTS

- There is robust evidence that behavioral signs of ASD can be detected by 1 year.
- Risk markers extend from atypical social communication to motor delays.
- Unusual *trajectories* of language and cognitive skills are reported in ASD.
- A combined behavioral and biomarker approach may help with early detection of ASD.

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ABSTRACT

Earlier identification and diagnosis of autism spectrum disorders (ASDs) can improve opportunities for children to benefit from intervention and lessen the burden on concerned parents. This review summarizes current knowledge about early signs of autism. Convergent data from both retrospective studies and prospective studies of high-risk infants indicate that ASD symptoms emerge in the first two years of life, affecting multiple developmental domains, mapping onto symptom dimensions consistent with current diagnostic frameworks including social-communication, and repetitive interests/behaviors but also extending to motor delays and atypical regulation of attention and emotion. Recent findings have shed new light on patterns of symptom onset and progression, and promise to inform early detection and diagnosis. Further attention to effective application of new findings and related challenges in building health system capacity to ensure timely access to specialized assessment and interventions is needed to fully realize the promise of improved outcomes resulting from this research.

Contents

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1. Introduction

The clinical and etiologic heterogeneity of children with autism spectrum disorders (ASD) contribute to the complex challenges associated with developing a comprehensive early detection strategy. However, it is essential to develop effective approaches to identify and diagnose children with ASD early in life. ASD is one of the most prevalent forms of developmental disability internationally, with current estimates at over 1 in 100 children [1,2]. Earlier diagnosis creates opportunities for children with ASD to benefit more fully from intervention; Dawson's [3] theoretical model goes as far to suggest the possibility of even *preventing* the full manifestations of ASD by taking advantage of early brain plasticity and potentially modifiable abnormalities in reward circuitry early in development [3]. Gains through early intervention can enhance adaptive and cognitive functioning (e.g., [4]) and may ultimately reduce the considerable family and societal costs related to ASD across the lifespan [5,6]. Earlier diagnosis also allows parents to be better informed about recurrence risk to later-born children, and better able to monitor for early signs of autism [7] and other related concerns [8].

This review is aimed at providing a detailed summary of current knowledge of early signs of ASD, from studies across a range of methodologies. Implications for underlying developmental processes and their relation to the emergence of ASD diagnostic features during infancy will be discussed, as will implications for clinical practice and future research.

1.1. Methodological considerations

Research examining early development in ASD has shifted over the past several years from mainly retrospective designs (i.e., through parent report or by examination of early home videos) to prospective longitudinal studies of at-risk infants, generally those with an older sibling with ASD [9]. While retrospective research has generated important insights that have informed current early detection strategies [10], there are some limitations inherent in such study designs. Parental reports of early symptoms of ASD are subject to recall biases; for example, early behaviors more closely related to later manifestations of ASD may be more easily recalled. Pre-diagnostic home videos provide more objective information regarding early behaviors and opportunities for standardized coding, but may be subject to other biases related to sampling. For example, children may be recorded as they are demonstrating a new skill or to commemorate a special event, rather than for the purpose of capturing a more representative range of behaviors. Indeed, the contexts from which behaviors are sampled by home videos vary, both within and across studies, which makes it more difficult to draw conclusions from the literature as a whole [11]. It is important to acknowledge that home video analyses continue to generate important insights; for example, recent studies focusing on behavior less subject to sampling biases (e.g., symmetry of movement [12,13]; see Section 2.4.1 for details) have raised intriguing hypotheses regarding the early motor system in ASD. However, over the past several years, prospective research designs focused on high-risk infants have been increasingly applied to study early development in ASD, with unique methodological advantages. Using this approach, standardized measures can be obtained early in development and over time, generating longitudinal data to map initial trajectories of symptom emergence. Increasingly, behavioral data has been supplemented by experimental measures (e.g., eye tracking, evoked brain responses) which can only be obtained prospectively, thus yielding additional insights regarding underlying developmental processes as well as potential biomarkers that might ultimately contribute to early detection [14]. That said, prospective studies are not without potential methodological limitations. First, affected children from multiple incidence sibships may not be fully representative of all children with ASD. Second, it is difficult to identify comparison groups of infants who are high-risk for developmental delays in prospective research, as risk factors for idiopathic developmental delay (by definition) are difficult to identify, and findings from groups with known risk factors (e.g., Down syndrome) may not generalize to other delayed children. However, prospective studies involving community-referred samples of infants who failed a broad developmental screening have allowed researchers to compare the profiles of infants with ASD to those of infants with other delays.

This review includes a synthesis of published findings that differentiate ASD from typical development and from developmental delay. We summarize these findings by category of behavior (combining early social and communicative features, in accordance with proposed criteria for DSM-5; [15]) and study design (retrospective vs. prospective).

2. Review findings

2.1. Social-communication

2.1.1. Retrospective studies

Retrospective parent report [16–23] and home-video studies [24–39] have found that infants later diagnosed with ASD can be distinguished from infants with typical development (TD) in the first two years of life based on early social-communicative behaviors. Retrospective parental reports, by questionnaire or structured interviews have tended to focus on timing and broad categories of concern (such as speech delay and reduced social-emotional response) and have lacked control groups [16–23]. These studies, mainly published in the 1980s and 1990s, provided powerful evidence that symptoms were present long before many children with ASD were clinically referred, but were generally not designed to characterize specific risk markers. Home video analyses took the field a step forward by using standardized criteria and in more recent studies, incorporating comparison groups of typically developing (TD) and/or developmentally delayed (DD) children, to determine what behavioral features in the first two years of life differentiate infants later diagnosed with ASD (see Table 1 for summary). Coding schemes have progressed from qualitative clinical ratings (e.g., Infant Behavior Summarized Evaluation by Adrien et al. [24]; also see [27,35] in Table 1) to quantitative coding of operationally defined behaviors [25,29,36,40,41].

As summarized in Table 1, several home video analyses have reported that by age 12 months children with ASD can be differentiated from those with typical development (TD) by differences in social communication behaviors. These studies report evidence of reduced/atypical orienting to people, or specifically, people's

Table 1
Home video studies assessing early social communication and/or repetitive behaviors.

First author and year of publication	Sample	Measurement of behavioral Signs	Main findings
Adrien et al. (1993)[a] [24]	• 12 children with AD aged 2.0–16.0 years and DQ 12–105	• Infant Behavior Summarized Evaluation (IBSE) scale: 33 behaviors on 5-point scale, independently rated by 2 psychiatrists blind to group.	• Items rated more commonly in autism vs. control group in first year: poor social interaction, no social smile, lack of appropriate facial expressions, hypotonia, easily distracted
	• AD diagnoses based on DSM-III-R	• Videos ranging in length from 10 to 80 min, "recorded by parents to preserve important events of their infants' first years". Only 4 had sound.	• Items rated more commonly in autism vs. control group in second year: ignores people, prefers aloneness, poor social interaction, no social smile, no eye contact, lack of appropriate facial expressions, lack of appropriate gestures, too calm, hypoactivity, hypotonia, easily distracted, unusual postures, no expression of emotions
	• 12 TD control children, no ASD symptom or IQ data reported		
Osterling and Dawson (1994) [27]	• 11 children with ASD aged 2.10–6.0 years, 6 with IQ > 75	• Coding system developed for study, categories included: affective expressions, looking, gaze aversion, response to name, social touch responses, anticipatory postures, as well as repetitive and sensorimotor behaviors, coded blind to group	• Group differences (PDD vs. control) were detected for pointing, showing, looking at the face of another person and failure to orient to name. These 4 items correctly classified 10 of 11 children in each group
	• Clinical diagnoses (AD or PDDNOS) based on DSM-III-R and CARS	• Videos from age 9 to 12 months, edited to total 10 min length	
	• 11 control children, no ASD symptom or IQ data reported		
Baranek (1999) [25]	• 11 children with autism, diagnosed by DSM-III-R or DSM-IV, plus CARS	• Coding system developed for study, focused on typical social, affective, joint attention and other communicative behaviors, 'autistic-like' behavior (e.g., repetitive behavior, lack of social response), coded blind to group	• Group differences (autism vs. TD and DD) were detected for response to name; other items approached significance ($p < .10$): orientation to visual stimuli, social touch aversion and mouthing of objects. Discriminant function analysis correctly classified 10 of 11 children with autism
	• 10 children with DD (6 with Down syndrome)	• Videos of first birthday parties, ranged in length from 3 to 29 min. Frequency of observed behavior adjusted for length of video	
	• 11 typically developing (TD) control children		
Mars et al. (1998) [35]	• 25 children with AD ($n = 15$) or PPD-NOS ($n = 10$)	• Used coding system developed by Osterling and Dawson [27] (see above)	• Eight behaviors differed in frequency between ASD and TD groups: expresses words, follows verbal directions, looks at faces, looks at people, imitates vocalizations, points with gaze, alternates gaze, and shows objects
	• AD or PPD-NOS diagnosis by tertiary-level clinical team using DSM-III-R/DSM-IV and CARS	• Additional coding of social engagement and object engagement (duration of time over 1-min intervals coded)	• Reduced social engagement (AD, PDD < TD; $p < .05$) but similar levels of object engagement
	• 25 children with TD, no atypical social behavior on Revised Denver Developmental Questionnaire	• Home videos taken between 12 and 30 months; mean length did not differ between groups (absolute length not reported). Analyses not stratified by age	
Werner et al. (2000) [30]	• 15 children with AD ($n = 8$) or PPD-NOS ($n = 7$)	• Home videos between ages 8–10 mo coded for presence or absence of behaviors categorized as social (e.g., looking at others, orienting to name being called), communication (vocalizations), and repetitive behaviors	• At 8–10 mo main effect of diagnostic group for social behaviors ($p < .05$), after children with late-onset ASD ($n = 3$) were removed from analysis
	• Confirmation of AD or PPD-NOS based on DSM-III-R plus ≥30 score on CARS		• Infants with ASD less likely than infants with TD to orient when their name was called ($p < .05$)
	• 15 children with TD		• No group differences in repetitive behaviors
Maestro et al., 2001[26]	• 15 children with AD	• Coding system developed for early communicative behaviors	• Infants later diagnosed with AD, compared to TD group:
	• Confirmation of AD by symptom checklist based on DSM-IV plus met CARS criteria		• 0–6 months: less following others' pointing, anticipation of other's aim
	• 15 children with TD		• 6–12 months: less pointing to show, communicative gestures

Table 1 (*Continued*)

First author and year of publication	Sample	Measurement of behavioral Signs	Main findings
Maestro et al. (2002) [41]	• 15 children aged 3.5–5.6 (mean: 4.1) yr with AD (n = 7) or PPD-NOS (n = 8) • ASD diagnosis by symptom checklist based on DSM-IV plus met CARS criteria • 15 TD″ children with mean age of 4.7 years, matched for gender and age with ASD group	• Home movies at 0–6 months lasting at least 10 min • Rated frequency of 3 domains of social behavior: social attention (e.g., looking at people), social behavior (e.g., anticipating the other's aim), and nonsocial attention (e.g., "explorative activity with object")	• Between ages 0 and 6 mo, significant group differences in social attention and social behavior, including: • Less frequent looking at people (p < .001) • Less frequent vocalizing to people (p < .001) • Less frequent orienting toward people (p .> 01) • No group differences in interest and attention to non-social stimuli
Osterling et al. (2002) [28]	• 20 children aged 2.5–10 years with diagnosis of AD (n = 7) or PPD-NOS (n = 13). Further stratified into ASD + DD (IQ < 70; n = 14) and ASD + TD • ASD diagnoses based on DSM-III-R and CARS • 14 children with DD (IQ < 70) • 20 children with TD, adaptive behavior within 1SD of average	• Coding system developed for study, categories included: gaze, social, affective, motor, communication, joint attention behavior; coded by duration (relative to total time), except for discrete behaviors (e.g., pointing) coded by frequency • Video obtained from first birthday parties, variation in length not reported	• Group differences reported (p < .05): • ASD + DD vs DD only: reduced 'orients to name' and 'looks at people' • ASD vs TD: reduced gestures, 'looks at object held by person', 'orients to name' and 'looks at people', and repetitive actions • *Note*: DD also showed reduced gestures, 'looks at object held by person' and repetitive actions compared to TD group
Maestro et al. (2005) [29]	• 15 children aged 3.5–5.2 years with AD diagnosis • ASD diagnosis by symptom checklist based on DSM-IV plus met CARS criteria • 13 TD children with mean age of 4.7 years	• Social attention behaviors assessed: looking at people, orienting toward people, smiling at people, vocalizing to people • Nonsocial attention behaviors assessed: looking at objects, orienting toward objects, smiling at objects, vocalizing to objects	• From each group, home movies lasting at least 10 min coded by blind observers for frequency of behaviors via an 8-item "grid" for assessment of social and nonsocial attention • Between ages 0 and 6 months, significant group differences in social attention (high scores in social vs. nonsocial stimuli in "typical" infants) • Between ages 7–12 months, no group differences in social or nonsocial attention; but behaviors re: attention to nonsocial stimuli increased in both AD and typical groups but "more evident" in the former
Werner and Dawson (2005) [36]	• 36 children with diagnosis of AD (n = 28) or PPD-NOS (n = 8); stratified into 'early onset' (n = 21) and 'regressive onset' by parent report on ADI-R • ASD diagnoses based on ADI-R, ADOS and DSM-IV • 20 children with TD	• Coded frequency of 7 behaviors: language, joint attention, orienting to name, positive affect, repetitive behavior and toy play • Video obtained from first and second birthday parties	• At 12 months, 'early onset' group had reduced declarative pointing compared to TD group, and 'regressive onset' had more complex babbling than 'early onset' group • At 24 months, both 'early onset' and 'regressive onset' ASD groups had reduced language, joint attention and orienting to name compared to TD • At 24 months, no differences between the two ASD groups; both showed evidence of reduced use of social gaze from 12 to 24 months
Colgan et al. (2006) [40]	• 21 children later diagnosed with AD • AD by DSM-III-R or DSM-IV and CARS • 14 children with TD	• Gestures coded from home videos showing infant interacting with adult, edited to 5 min segments • Videos from ages 9–12 months	• AD group demonstrated decreased variety (but not total frequency) of social interaction gestures compared to TD group
Clifford et al. (2007) [33]	• 15 children with AD diagnosis • ASD diagnoses based on DSM-IV and CARS • 15 children with DD, 'global delay' or 'language problems' based on clinical assessment • 15 children with TD, 'no history of developmental or language problems'	• Coding system developed by authors, 10 items for frequency and 7 items for quality of social behavior • Videos taken from 12 to 24 months, child with adult, mainly documenting special occasions • Length of videos 12–180 min, edited to 2× 5 min segments	• Group differences (p < .01 to account for multiple comparisons) • AD vs. TD: reduced eye contact, gaze aversion, response to name, showing, positive affect, peer interest, anticipatory postures • AD vs. DD: gaze aversion, showing, peer interest

Table 1 (*Continued*)

First author and year of publication	Sample	Measurement of behavioral Signs	Main findings
Clifford et al. (2008) [31]	• 18 children with AD diagnosis	• Coding system developed by authors, frequency counts of joint attention and other social behaviors	• Overall AD vs. control group differences ($p < .01$ to account for multiple comparisons)
	• ASD diagnoses based on DSM-IV and CARS	• Videos taken from 0 to 24 months, edited into 10 min segments covering 0–5, 6–11, 12–17, 18–24 months, although data provided for 0–11 and 12–24 months, and analyses limited to overall group comparisoins	• Reduced initiation of joint attention, joint attention quality, initiating requests, eye contact
	• 9 children with DD (global or language delay) or TD as combined control group • Subset of larger sample (AD = 36, control = 27) participating in parent report study who had available home videos		• Trend for reduced response to name and affect quality ($p < .025$)
Ozonoff et al. 2011[37]	• 52 children aged 23–59 months with AD	• Frequency counts of 4 social behaviors coded as per Werner and Dawson [36]: looks at people, smiles at people, language and point (to show or request)	• Three trajectories identified within AD group: 'early onset' ($n = 20$), 'regression' ($n = 20$), and 'plateau' ($n = 13$). The first two AD trajectories differed from the TD trajectory (inclining) by baseline and linear change.
	• AD diagnosis based on ADOS, ADI-R and DSM-IV	• Coded all videos available from 6 to 24 months	• Limited agreement between parent-report and home video based classification of trajectories (kappa = .11; $p > .10$)
	• 23 TD children aged 12–42 months, no evidence of delay on MSEL or AD symptoms on ADI-R or ADOS	• Latent trajectories identified using longitudinal analysis methods	
Watson et al. (2013) [39]	• 43 children aged 2–7 years with AD	• Frequency count of communicative gestures, classified by function: social interaction (e.g., in a social game such as peek-a-boo), behavioral regulation (e.g., reaching to be picked up), joint attention (e.g., showing, pointing)	• At 9–12 months, AD group had fewer behavioral regulation and joint attention gestures than the TD group (but no significant difference between AD and DD groups)
	• AD diagnosis based on DSM-IV, supported either by ADOS/ADI-R or CARS	• 5 min segments × 2 for two age intervals: 9–12 months and 15–18 months	• At 15–18 months, AD group had fewer joint attention gestures than the TD and DD groups difference between AD groups
	• 30 children with DD: IQ < 70 with at least 2 domains < 1.5 SD below mean, CARS < 25	• Also examined developmental change across the two age intervals	• No group by time interactions over gesture type
	• 36 TD children s, no evidence of delay on MSEL or AD symptoms on CARS		

AD, autistic disorder; PPD-NOS, pervasive developmental disorder-not otherwise specified; ASD, autism spectrum disorders; TD, typical development; DD, developmental delay; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; CARS, Childhood Autism Rating Scale; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; MSEL, Mullen Scales of Early Learning; VABS, Vineland Adaptive behavior Scales.

[a] Preliminary analyses from this sample can be found in two previous publications: Adrien et al., 1991 [34]; Adrien et al., 1992 [32].

faces [24,29], despite no group differences in studies that assessed orienting to non-social stimuli [29,35,41]. Other replicated findings include lack of responding to name [25,28,30], reduced eye contact [31], reduced positive affect including social smiling [24,26,29,30], and fewer communicative gestures including declarative pointing [26–28]. Few home video studies have reported on children younger than 8 months. Maestro et al. [26,29] described reduced directed vocalization and looking at people in children with ASD by 6 months; Ozonoff et al. [37] also reported evidence of reduced social orienting at 6 months.

A small number of home video studies that have specifically reported on the second year of life provide further evidence of reduced social interest in toddlers later diagnosed with ASD, including ignoring people and preferring to be alone [24] and reduced peer interest [33]. Other findings in 24 month olds are similar to those reported at 12 months, including atypical/reduced social orienting including poor eye contact [24,33], reduced orienting to name being called [24,33,35] and reduced spontaneous expression of positive affect [24,33]. Findings on responsive smiling are less consistent. Adrien et al. [24] reported differences between 12- and 24-month-olds with ASD and TD based on global clinical ratings, whereas Clifford and colleagues [31,33] did not detect group differences in social smiling at that age in two independent samples, based on frequency counts.

Including comparison groups of children with developmental delays (DD) has allowed some home video studies to distinguish behaviors that are ASD-specific from those that are shared by ASD and DD. Baranek [25] and Osterling et al. [28] found that children with ASD exhibit reduced response to name, and reduced gaze to faces compared to children with DD at 9–12 months. In other respects, infants with DD have been reported to be more similar in respect to social behavior to infants later diagnosed with ASD than are TD infants. For example, Osterling et al. [28] reported that infants with ASD did not differ in frequency of gestures and vocalizations from infants with DD at 12 months; Watson et al. [39] also found no significant difference across gesture type between AD and DD groups at 9–12 months. As well, Clifford et al. [33] detected less robust differences in quality of eye gaze, shared positive affect, and participation in social games between ASD and DD groups in the second year, relative to the ASD and

TD comparisons. However, there is evidence that ASD follows a different developmental course by age 2 compared to DD in respect to gaze and affect-related behaviors. Clifford and Dissanayake [31] reported that infants with ASD had declining eye contact and increasingly atypical affective expression from the first to second year of life, whereas those with DD maintained similar levels of these behaviors across this period. In addition, children with ASD showed little change in gaze shifting and social referencing over time, whereas children with DD improved by age 2 [31]. Clifford et al. [33] also reported reduced interest in peers, and reduced showing in 2-year-olds later diagnosed with ASD compared to those with DD. While Clifford et al. [33] reported modestly reduced sharing of *positive* affect in ASD compared to DD, 2 year-olds with ASD and DD had similar levels of expressed *negative* affect.

Reduced communicative gestures also discriminated ASD from DD at age 2 [33,35]. Clifford and Dissanayake [31] found that children with ASD were delayed, compared to children with DD, in their ability to follow a point, and to point to request or comment. Children with ASD showed little change in their ability to follow a point and to point to request from the first to second year of life, while those with DD improved. Watson et al. [39] also reported fewer joint attention gestures at 15–18 months in children with ASD ($n = 43$) compared those with DD ($n = 30$). Werner et al. [38] compared preschool children with ASD ($n = 74$) to those with DD ($n = 34$) and TD ($n = 30$), based on parent report on the Early Development Interview which covered multiple aspects of social-communication. While differences between ASD and TD groups were identified in the first year, differences between ASD and DD groups were not detected until the second year: 13–15 months for social behaviors (e.g., responsive smiling) and 19–24 months for communication (e.g., use of gestures).

Home video analyses have also been used to examine the phenomenon of developmental regression in ASD. Werner and Dawson [36] analyzed home videos taken around 12 and 24 months (in most cases, first and second birthday parties) in 15 children with ASD and regression, 21 children with 'early onset' ASD (symptoms in the first year and no history of regression, based on parent report), and 20 children with TD. Regression was assessed by the Autism Diagnostic Interview-Revised at 3 years of age or later and was considered to be present if the parent reported loss of language, social-communication or other skills in the second year. The ASD with regression group demonstrated similar levels of joint attention behaviors and vocalization as the TD group at 12 months, but by 24 months of age displayed fewer instances of word use, vocalizations, declarative pointing, social gaze, and orienting to name. In contrast, the 'early onset' group had fewer joint attention and communication behaviors compared to the TD group at both 12 and 24 months. Ozonoff et al. [37] analyzed social-communication behavior of 52 children with ASD from home videos taken between ages 6 and 24 months. The early home videos of 23 TD children ($n = 23$) were coded for comparison. The authors identified 3 subgroups within the ASD sample with developmental trajectories distinct from children with TD. The first subgroup ($n = 20$; 38.5%) was characterized by lower levels of social-communication throughout the assessment interval beginning at 6 months and was termed 'early onset'. The second ($n = 20$; 38.5%) demonstrated typical (even increased) social-communication behavior at 6 months which then decreased steadily to 24 months, and thus was termed 'regression'. The third ($n = 12$; 23%) showed typical levels of social-communication at 6 months but these remained at a similar level to age 24 months (in contrast to the TD group which demonstrated steady increases), and was termed 'plateau'. Although these trajectory patterns corresponded well with those previously described by parents (particularly regression), there was surprisingly poor agreement between classification based on analyses of home videos and parents' retrospective reports at age 3 years, which did not exceed that expected by chance (weighted kappa = .11; $p = .29$; [37]).

2.1.2. Prospective studies

Prospective studies of HR infants have extended findings from retrospective research, demonstrating clear differences in trajectories of early social and communicative behaviors. These studies have also yielded insights about how early manifestations of ASD may exist on a continuum of a broader range of social communication deficits, and that even within ASD, there may be significant heterogeneity in respect to early signs and developmental course.

To characterize early behavioral trajectories, Ozonoff et al. [42] coded frequency of gaze to faces, directed social smiles and directed vocalizations per minute, and the quality of social engagement, during the administration of the Mullen Scales of Early Learning (MSEL) in HR and LR infants at repeated time points between 6 and 36 months of age. They reported that infants subsequently diagnosed with ASD were indistinguishable from TD infants at 6 months, then showed declining trajectories to age 36 months, whereas TD infants showed stable (gaze to faces and quality of social engagement) or increasing (social smiles, directed vocalizations) trajectories over the same time period. Zwaigenbaum et al. [43] also reported that overt differences in social behavior associated with ASD in HR infants emerge in the latter half of the first year. No social-communication markers specific to ASD were identified at 6 months, whereas several robust differences were observed at 12 months (decreased social interest and affect, social smiling, orienting to name, and imitation, as well as atypical eye contact), as coded by the Autism Observation Scale for Infants (AOSI; [44]). In a subsequent case series of the first 9 children with ASD ascertained from the HR sample reported by Zwaigenbaum et al. [43], Bryson et al. [45] described a consistent pattern of apparently typical social responsiveness, shared enjoyment and appropriate eye gaze at 6 months, followed by reduced social engagement, shared enjoyment and non-verbal communication by age 12 months. More recent studies have reported subtle social-communication differences as early as 6 months in HR infants compared to LR infants. For example, Bhat et al. [46] reported reduced spontaneous social orienting in HR compared to LR 6-month-olds, despite comparable responses to caregiver initiated social bids. Early infant-parent interactions may also distinguish HR from LR infants: Yirmiya et al. [47] reported less synchronous interactions, and Wan et al. [48] reported less 'liveliness' (physical activity during social interactions) in HR compared to LR infants. However, these behavioral findings are based on group differences between HR and LR infants irrespective of subsequent outcomes, and recent data from Landa et al. [49] indicate no differences in social behaviors at 6 months associated with ASD outcomes within a large HR cohort ($n = 204$), with divergence in trajectories between diagnosed and non-diagnosed groups from 6 to 36 months, similar to the pattern reported by Ozonoff et al. [42]. There is growing evidence of atypical face processing as indexed by eye gaze patterns and or evoked response profiles in HR relative to LR infants at age 6–10 months [50–52]; see review by Elsabbagh (in this issue), including one recent study which found that evoked responses to dynamic gaze shifts in HR infants were predictive of ASD at 36 months [53]. However, to date no prospective study which has correlated early behavior to subsequent outcomes has found that infants later diagnosed with ASD can be identified on the basis of atypical social-communication prior to 12 months [42,43,49,54].

Consistent with Ozonoff et al. [42] and Landa et al. [49], several other prospective studies have identified social communication behaviors predictive of ASD early in the second year of life. Reduced shared positive affect is a highly replicated risk marker for ASD in HR infant siblings (for example, see Landa et al. [54] and Brian et al.

[55]) as well as at-risk infants identified by population screening for communication delays, as reported by Wetherby et al. [56]. Reduced response to joint attention (RJA) at 15–18 months is also a robust predictor of ASD diagnosis [57,58], but mild deficits are not specific to ASD, as there are positive correlations with a broader continuum of social-communication impairment at 34 months [58]. Prospective studies have also found that by 12–14 months, infants later diagnosed with ASD show delays in the acquisition of communicative and symbolic gestures [43,59,60], reduplicated babbling [59], and directed vocalizations [42]. Reduced orienting to name at 12–18 months of age is also common among HR infants subsequently diagnosed with ASD [43,55,61].

Few published prospective studies have been sufficiently large to examine variation in early social-communication symptom trajectories *among* infants with ASD outcomes. Landa et al. [54] reported on 15 early- and 13 later-diagnosed children with ASD from a HR sibling cohort (identified at 14 and 24 months, respectively) as well as 68 HR siblings not diagnosed with ASD and 17 LR controls. They found extensive differences between the early diagnosed and non-diagnosed groups at 14 months with respect to early joint attention behaviors (including initiating and responding to joint attention), shared positive affect and gestural communication, which persisted to age 24 months. In contrast, the later diagnosed group truly appeared relatively asymptomatic at 14 months, differing from non-diagnosed HR infants only on the basis of frequency of gaze shifts, whereas, many symptoms were present by 24 months, leading to suspected ASD diagnosis. Preliminary data from the Zwaigenbaum and Bryson cohort [43,45] also indicate significant heterogeneity in early symptom trajectories indexed by the AOSI among HR infants diagnosed with ASD at age 3, with one subgroup demonstrating inclining scores between 6 and 18 months, and two other subgroups with stable or declining scores over that interval. In this study, trajectory membership was correlated with severity of ASD symptoms and cognitive impairment at age 3, consistent with the proposed subgroupings from a case series of HR infants with ASD outcomes reported by Bryson et al. [45].

2.2. Language and cognitive development

2.2.1. Retrospective Studies

Delays in spoken language are among the most common symptoms that prompt initial medical consultation for possible ASD [7,62] and are frequently identified, in retrospect, as among the earliest parental concerns [16–20]. Home video analyses also provide some evidence that language delays can be detected in the second year (e.g., by general clinical ratings of vocalization and word usage [35]). However, the sampling approach of most home video analyses, including selection of brief video segments, often over an extended age range, is not likely to provide a comprehensive assessment of expressive and receptive language skills at a given point in time. Moreover, language production may be influenced by contextual factors surrounding the particular circumstances of the video.

2.2.2. Prospective studies

Following up on parents' retrospective reports of early delays, prospective research designs have incorporated standardized measures to further delineate early language and cognitive trajectories in ASD. Zwaigenbaum et al. [43] reported that 12-month-old HR infants classified with autism at 24 months had lower expressive and receptive language scores on the Mullen Scales of Early Learning (MSEL) than HR infants not diagnosed with ASD and LR infants. Landa and Garrett-Mayer [63] conducted similar group comparisons on MSEL scores from 6 to 24 months and reported that HR infants with ASD at 24 months scored lower on expressive and receptive language at 14 months (but not at 6 months) than non-ASD HR and LR groups, with some evidence of decreasing standard scores from 14 to 24 months. Bryson et al. [44] also reported declines in MSEL standard scores over the second year in some (but not all) HR infants diagnosed with ASD by age 3, indicative of slowed acquisition of new skills. Landa et al. [64] recently reported latent growth class analyses of MSEL subscale scores in HR and LR infants from ages 6 to 36 months. HR infants with ASD were overrepresented in a trajectory class characterized by 'developmental slowing'; that is, decreasing T scores; raw scores were not reported. Although 30 of 52 (53.3%) were classified into other classes (one characterized by transient receptive language delays, and two others characterized by average or above average language skills), the developmental slowing trajectory was highly specific to ASD (>90%). In a related study, Landa et al. [49] reported that developmental slowing (or even frank skill loss) occurs in both early (i.e., by 14 months) and later (24-month-old) diagnosed children with ASD. Evidence of similar developmental slowing in non-verbal cognitive skills (the MSEL 'Visual Reception subscale) was also reported in these studies, with substantial decline in standard scores [44,49,63,64]. Barbaro and Dissanayake [65] compared children identified through community screening with ASD (stratified into those meeting full criteria for autistic disorder and those who did not) and DD (some with global delays, some with specific language delays). Children with autistic disorder at age 2 had more severe expressive and receptive language delays at 18 and 24 months as well as evidence of developmental slowing over that interval (based on a significant time by group interaction), compared to other ASD and DD groups. Thus, developmental slowing in the second year may have clinical utility as a risk marker in both HR and community samples, albeit with specificity to autistic disorder rather than other ASDs [65].

2.3. Repetitive interests and behaviors

2.3.1. Retrospective studies

Although repetitive interests and behaviors have been well-characterized in children diagnosed with ASD as young as 2 years of age [66–68], there is relatively little information from retrospective studies on how such symptoms are expressed earlier in development. Baranek [25] analyzed home videos taken at 9–12 months of 11 children with ASD, 10 with DD, and 11 TD children, and reported that motor/object stereotypies and atypical sensory modulation, along with social-communication deficits (e.g., response to name, anticipatory postures; see Section 2.1.1) contributed to a behavioral profile that discriminated children with ASD and DD from those with TD. However, infants later diagnosed with ASD demonstrated *less* visual fixation on objects compared to those with DD, and in general, repetitive behaviors did not discriminate ASD and DD groups [25]. Similarly, in the analysis of first birthday parties by Osterling et al. [28], 12-month-olds later diagnosed with ASD ($n = 20$) had similar levels of repetitive motor actions as those with DD ($n = 14$), although both groups exhibited these behaviors more frequently than TD children ($n = 20$). In a related study, Werner and Dawson [36] analyzed home videos taken around 12 and 24 months (i.e., at 1st and 2nd birthday parties) and reported that ASD (both early and regressive onset) and TD groups engaged in repetitive motor behaviors for a similar percentage of time). In an earlier study, Werner et al. [30] also found no evidence for increased repetitive behaviors in children with ASD compared to TD controls at 8–10 months. Notably, parents' retrospective reports have suggested that stereotypic behaviors may emerge prior to diagnosis, but generally in the second rather than the first year [18–20]. Thus, retrospective research designs would suggest that repetitive behaviors are not a consistent feature of ASD, generally do not emerge until after the first birthday, and even then, are not

specific to ASD but rather may be observed in children with other developmental delays.

2.3.2. Prospective studies

Prospective studies of at-risk infants have more consistently identified early repetitive behaviors predictive of subsequent ASD diagnoses. Wetherby and colleagues [56,69,70] compared ASD and age-matched language delayed (LD) groups (12–23 months; mean age = 21 months) ascertained by screening in community settings using the Infant Toddler Checklist (ITC), a component of the Communication and Symbolic Communication Scales-Developmental Profile (CSBS-DP; [71]) and assessed using standard diagnostic measures including the Autism Diagnostic Observation Schedule (ADOS) at age 2–3 years. A comparison group of TD children were randomly selected from among screen negative children, age- and sex-matched to the ASD group. In the first report on this cohort, Wetherby et al. [56] found that repetitive movements (either with body or with object) were more commonly observed in the ASD group (n = 18) than the other two groups (*n*'s = 18). A follow-up study in an expanded sample of children indicated that the ASD group ($n = 50$) demonstrated higher frequency and duration of repetitive behavior with objects and with body, compared to both the LD ($n = 25$) and TD ($n = 50$) groups, based on quantitative micro-coding [70] and a clinical rating system, the Repetitive Stereotyped Movements Scales [72], both completed from video. In a subsequent study [69], the ASD group ($n = 50$) was compared to TD infants ($n = 50$) matched on *developmental* age (about 14 months), rather than chronological age (21 months). The findings were largely the same as in the Watt et al. [70] study of chronologically age-matched groups, with the exception that the younger TD group more frequently banged the counter surface with their hands. Children subsequently diagnosed with ASD demonstrated higher frequencies of other repetitive behaviors with objects (such as rocking/flipping, swiping, rolling and clutching) and with body (rubbing and stiffening) compared to the developmentally matched infant group [69].

Similar findings come from prospective studies of HR infant siblings of children with ASD. Ozonoff et al. [73] reported that 12-month-old HR infants with ASD ($n = 9$) were no different from DD ($n = 10$) and TD ($n = 47$) infants in typical uses of objects such as throwing and mouthing, but did differ from both groups in atypical uses such as rotating, spinning and unusual visual exploration. Using the performances of their TD group as a normative sample, Ozonoff et al. [73] generated *z*-scores for atypical uses of objects for each infant. The majority (78%) of the children with ASD performed more than 2 SD above the mean on at least one atypical object use, compared to roughly half of those with DD and a quarter of the TD children. In particular, almost all of the infants with ASD showed unusual visual exploration, with a group mean *z*-score greater than 4. Atypical sensory-oriented behaviors at 12 months (including intense visual inspection) were also identified as an early risk marker of ASD in 74 HR infants assessed by Zwaigenbaum et al. [43], and described by Bryson et al. [45] in their initial case series of 9 HR infants diagnosed with ASD.

2.4. Motor development

2.4.1. Retrospective studies

Kanner [74], in his original case series, reported that severe social and communication delays contrasted with generally typical motor performance, observing that motor milestones were generally within normal limits and fine motor coordination was 'very skilful', although some patients had awkward gait and gross motor coordination deficits. Subsequent research has indicated that many school-aged children with ASD experience significant difficulties with balance, postural stability and timed movements [75,76]. However, until recently, there has been relatively little attention to atypical motor development during infancy as a potential diagnostic risk marker for ASD (see Table 2). Adrien et al. [24] compared the early home videos of 12 children with ASD and 12 typically developing children using a standardized behavioral coding scale, and reported that unusual postures, hypoactivity, and hypotonia were more common in the ASD group. Teitelbaum et al. [77] compared the early home videos of 17 children with ASD to a control group of typically developing infants filmed prospectively on an Israeli kibbutz. Infants later diagnosed with ASD were described as having several motor abnormalities in the first 6–9 months, including delayed righting and protective reflexes, asymmetric and unusual quality of movements (e.g., abnormal body position when crawling), in addition to delays in maturity of movements (e.g., head control and ability to weight bear on arms in prone position, and coordination of movements when walking). However, these findings were based on qualitative description of the ASD group rather than standardized ratings. No data on the controls were reported, and the analysis of motor behaviors did not appear to be blind to group. Ozonoff et al. [73] attempted to replicate findings from Teitelbaum et al. [77], developing and establishing the reliability of a standardized coding system to rate movement maturity, quality and protective reflexes from home videos taken in the first two years. Participants included 54 children with autism, 25 chronological and developmental-age matched children with DD and 24 developmental age-matched children with TD. Group differences in motor maturity were identified, with the children in the DD and autism (no regression) groups showing delays compared to the TD group in walking and weight bearing/stability in prone and supine positions. However, there was no evidence of movement abnormalities or reduced protective responses in children with autism compared to TD children; rather, it was the DD group who differed from the TD group in the first 2 years. Thus, Ozonoff et al. [78] concluded that some infants later diagnosed with autism experienced motor *delays* (i.e., when observed in a standing, supine or prone position) similar to those observed in infants with DD, but not *qualitative* movement abnormalities or reduced protective reflexes. Trajectory analyses also indicated that the delays persisted across the first two years for autism and DD groups, consistent with reduced scores on standardized motor measures reported in older children in both groups. Children with ASD could not be discriminated from those with DD based on motor development over the first 2 years [78].

However, recent research by Esposito, Muratori and colleagues has yielded intriguing qualitative differences in early motor functioning in ASD beginning in infancy, extending the work of Teitelbaum et al. [77] by applying rigorous measures of posture and movement to the analysis of early home videos (see Table 2). Esposito et al. [79] assessed 'static symmetry' (coded from single frames) and 'dynamic symmetry' (coded over 1 s intervals that included 4 frames) in 0- to 5-month old infants in a lying position. Home videos were coded using a standardized movement analysis system. Children with ASD exhibited lower levels of both static and dynamic symmetry than both DD and TD controls, and a subsequent cluster analysis suggested the potential to distinguish children with ASD on an individual basis from the other 2 groups by symmetry coding. Esposito et al. [12,13] also examined static and dynamic symmetry via gait analysis of children with ASD, DD and TD, using videos taken shortly after participants were walking independently. As in the previous study, there was evidence of positional asymmetry in toddlers subsequently diagnosed with ASD relative to both comparison groups. Some specific features identified during gait analysis (e.g., forearm rigidity) did not differentiate between ASD and DD, although global ratings from the authors' 'Walking Observational Scale' did differ between these groups [13]. Finally, Phagava et al. [80] reported differences in spontaneous general movements (i.e., fidgeting and writhing) based on

Table 2
Home video studies assessing early motor behaviors.

Teitelbaum et al. (1999) [77]	• 17 children with AD, based on parent-reported clinical diagnosis, recruited from Autism Society of America mailing/email list • 15 typically developing (TD) control children recruited prospectively from Israeli kibbutz	• Used Eshkol–Wachman Movement Analysis framework to assess lying, righting, sitting, crawling, standing, and walking, with special focus on posture and symmetry • Videos of children with AD sent by mail, from 0 to 5 years, findings described by age interval, but stratification process not reported • TD group also videos and analyzed, although findings not reported	• Findings in ASD group described qualitatively based on individual case studies, no explicit comparison to TD group • Asymmetry in various positions (e.g., lying) and movements (e.g., sitting, crawling), abnormal righting (e.g., while rolling from supine to prone), atypical dynamics of crawling and walking, qualitative evidence of motor delays
Ozonoff et al. (2008) [78]	• 54 children with AD, 26–61 months, diagnosis confirmed by DSM-IV, ADI-R and ADOS • AD group stratified into regressed (n = 28) and non-regressed, based on ADI-R • 25 children with DD, 24–56 months, development and age-matched to AD group • 24 children with TD, no evidence of ASD on ADOS, ADI-R	• Developed coding system: Infant Motor Maturity and Atypicality Coding Scales, rated motor maturity (when prone, supine, rolling, sitting, crawling, and walking) and protective responses (i.e., ability to right oneself following loss of balance when sitting, crawling and walking) • Aimed at replicating Teitelbaum et al. (1999) • All home videos taken from 0 to 24 months requested for analysis	• Group differences in motor maturity (ASD, DD groups delayed relative to TD group, no differences between ASD and DD groups) • No evidence of qualitative abnormality in posture, movement nor protective reflexes in ASD group • DD group had qualitative abnormalities in prone and sitting position when compared to TD and AD-regressed groups
Esposito et al. (2008) [12]	• 16 children age 20 ± 2 months with AD (mean IQ = 55) • AD diagnosis based on DSM-IV and ADOS • 10 children age 21 ± 2 months with DD (mean IQ = 55) • 13 TD children age 20 ± 2 months, no medical or developmental concerns	• Used 'Walking Observation Scale' (WOS; 11 items coding gait on 3 axes: foot, arm and global movement based on % time) • Videos taken within 6 months of independent walking, mainly from family play situations and/or special events (e.g., birthday party) • Available video edited to one 5-min segment per participant	• AD group had higher overall and subscale scores on WOS, indicating greater atypicality with respect to foot, arm and global movement • Item level analyses indicated 'waddling gait' and lack of arm-foot oppositional movements more often in the AD group compared to DD and TD groups
Phagava et al. (2008) [80]	• 20 children with AD • AD diagnosis based on DSM and CARS • 20 children with TD age matched to AD group	• Assessed 70 video clips across the 40 participants, ranging in length 31–231 s • Global rating of 'general movements' (GM; refers to spontaneous movements) • Writhing movements (at 0–8 weeks – available for 7 in each group): rated as normal, poor repertoire, cramped-synchronized or chaotic • Fidgety movements (at 9–21 weeks–available for 17 in each group): rated as normal, absent or abnormal	• Overall 'GM' optimality (based on both writhing and fidgeting) poorer in AD group • AD group described as more often having 'poor repertoire' writhing movements vs. controls (70% vs. 12.5%) and absent or abnormal fidgety movements (50% vs. 11%), but these differences did not reach statistical significance due to small sample size
Esposito et al. (2009) [79]	• 18 children age 20 ± 2 months with AD (mean IQ = 55), stratified into early (n = 10) and late (n = 8) onset groups • AD diagnosis based on DSM-IV, ADOS/ADI-R and CARS • 12 children with DD • 18 TD children, no medical or developmental concerns	• Used Eshkol–Wachman Movement Notation (EWMN) to assess Positional Pattern for Symmetry during Lying (PPSL); codes for all possible symmetric positions of a body in supine position as seen in a 2D image • Static Symmetry (SS; based on single video frame) and Dynamic Symmetry (DS; based on groups of 4 frames over 1 s window) were coded • Videos from ages 12–21 weeks edited to create 3 min segment for each child	• Less SS and DS in AD group compared to TD and DD groups (p < .05) • Cluster analysis yielded 'lower level of symmetry' (n = 8) and 'higher level of symmetry' (n = 38) groups; the former was comprised entirely of children with AD

Table 2 (*Continued*)

Esposito et al. (2011) [13]	• 20 children with AD (mean IQ = 61) • AD diagnosis based on DSM-IV, ADOS, ADI-R and CARS • 15 children with DD (mean IQ = 63) • 20 TD children, no medical or developmental concerns (mean IQ = 102)	• Used 'Walking Observation Scale' (WOS; see Esposito et al. [12]) and Positional Pattern for Symmetry, which assesses static and dynamic symmetry during gait • Selected first available video showing child walking without assistance, and all other video within 2 week window • Available video edited to one 5-min segment per participant	• AD group showed greater static and dynamic asymmetry during walking than DD and TD groups • AD group had higher scores on WOS indicating greater atypicality with respect to foot and arm (but not global) movements

analysis of home videos taken in the first 5 months in ASD compared to TD infants (no DD comparison group in this study). These findings raise interesting questions about whether abnormalities in the motor system in ASD are expressed as underdevelopment of postural control during infancy [13] although await replication by other groups and in larger samples.

2.4.2. Prospective studies

Prospective studies of HR infants have further characterized motor findings predictive of ASD outcome. In their original report describing early development in 87 HR infants, Landa et al. [63] found that children with ASD had lower fine motor (FM) and gross motor (GM) scores on the MSEL compared to non-diagnosed infants at 14 and 24 months, but not at 6 months. Similarly, Zwaigenbaum and colleagues [55,43] have reported that MSEL FM and GM scores distinguish children with ASD from other HR infants at 12 and 18, but not 6 months, and Ozonoff et al. [42] reported FM differences emerging at 18 months. Recent trajectory analyses by Landa and colleagues in a larger sample of HR infants ($n = 204$) followed to 36 months are consistent with their original findings, at least on the MSEL [49,64]. However, qualitative assessment of motor skills by the same group suggest abnormalities in postural control (specifically, head lag) may be detected as early as 6 months. Flanagan et al. [81] reported that 9 of 10 (90%) HR infants diagnosed with ASD at 30–36 months had pronounced head lag at 6 months, compared to 13 of 30 (43%) non-diagnosed HR infants ($p = .002$). Notably, within the non-diagnosed group, 13 had non-autistic social communication delays at 30–36 months, 7 of whom had head lag at 6 months (54%), which is not significantly different than the rate in the ASD group. Moreover, in a related study using the Alberta Infant Motor Scales in a subsample of the Flanagan et al. [81] cohort, motor delays at 6 months were predictive of communication delays at 18 months across the HR group (i.e., not limited to children with ASD) [82]. Further clarification is needed as to whether motor delays at 6 months are specific to ASD or shared by a broader group of HR infants with social-communication symptoms by age 3. In their longitudinal study of HR and LR infants followed from 5 to 14 months, Iverson and Wozniak [59] reported that the HR group demonstrated relative postural instability and had a higher proportion of infants with delayed onset of independent sitting and walking. Early motor delays may also be evident in community samples of children with ASD. Bolton et al. [83] recently reported that fine motor behaviors were among a larger set of parent-report items on a general developmental screener that were informative for risk of ASD at 6 months.

2.5. Self-regulation and temperament

2.5.1. Retrospective studies

Difficulties with regulating emotional states (i.e., reduced positive affect, irritability, difficulty soothing) as well as biological functions (e.g., sleep and feeding) are among the earliest and most pronounced features described in retrospect by parents of children with ASD [16–18]. Retrospective analyses of early home videos have also revealed reduced positive affect in children with ASD compared to TD and DD groups during the first two years of life [25,33]. Findings are less consistent for negative affect [33] perhaps in part because parents may be less inclined to videotape their infant in that affective state. However, in one of the earliest descriptions of how ASD can manifest during infancy, Dawson et al. [84] provided a case report of a child who had been referred to a neurologist at 1 month of age due to feeding problems, and then demonstrated progressively reduced positive affect, increased irritability and hypersensitivity to auditory and tactile stimuli (as well as reduced social engagement) by 12 months of age.

2.5.2. Prospective studies

As noted in Section 2.1.2, a number of prospective studies have shown evidence of reduced expression of positive affect by the first birthday in high-risk infant siblings who are subsequently diagnosed with ASD, compared to non-diagnosed siblings and low-risk infants [43,58,54]. Moreover, the intense object-oriented visual fixations in children with ASD at 12 months reported in several prospective observational studies [43,45,56,73] also implicates potential abnormalities in early regulation of attention. With evidence of abnormal regulation of both affect and visual attention in the first year, the construct of temperament (defined as individual differences in reactivity and regulation; [85]) may provide a useful theoretical framework by which to understand early development in ASD.

Garon et al. [86] examined the relationship between prospective parental reports of temperament at 24 months, and 3-year outcomes in a sample of high-risk infant siblings ($n = 138$) and low-risk infants ($n = 73$). Using discriminant function analysis, they identified profiles that distinguished among siblings subsequently diagnosed with ASD, non-diagnosed siblings, and low-risk comparison infants. The first profile, which included low positive affect and increased duration of attention, was associated specifically with ASD at 36 months. The second, characterized by poor regulation of negative emotions, and difficulty with attention control (increased attention shifting) distinguished the two high-risk sibling groups from the comparison infants. In an earlier analysis involving the same (but smaller) sample, Zwaigenbaum et al. [43] reported reductions in observed positive affective responses and increased distress reactions in children with ASD at 12 months coded from the Autism Observation Scale for Infants compared to those with TD, consistent with concurrent parental report of temperament. Recently, Clifford et al. [87] examined parent-reported temperament in 54 HR and 45 LR infants, and found that reduced positive affect and increased perceptual sensitivity (although not increased negative affect) characterized HR-infants later diagnosed with ASD beginning at 7 months, with a similar profile of affect

and attentional differences compared to LR infants at 24 months as reported by Garon et al. [86].

3. Discussion

There is now robust evidence from both retrospective and prospective studies that behavioral signs of ASD can be detected early in infancy. Although as many as 50% of parents may recall concerns dating back to the first year [16–20], home video analyses and prospective studies of high-risk markers suggest that differentiation of children with ASD from typically developing and developmentally delayed peers occurs more robustly in the second year. Replicated risk markers include impairments in social communication (e.g., reduced social orienting/response to name, reduced joint attention behaviors), repetitive behaviors involving body movements and/or atypical use of objects (e.g., intense visual inspection and repetitive actions such as tapping and spinning), and atypical emotional regulation (reduced positive affect and more variably, increased negative affect). Particular patterns of developmental delay (language, extending to both words and gestures, and motor, particularly postural control) also appear to characterize infants subsequently diagnosed with ASD, although mainly based on comparisons with typically developing children rather than developmentally delayed children who do not have ASD. Several independent longitudinal studies have also implicated atypical developmental *trajectories*, characterized by a progressive reduction in age-appropriate social behaviors, as well as evidence of plateauing (slowed acquisition) of language and non-verbal cognitive skills. These findings point to the feasibility of earlier diagnosis, at least in a subgroup of children with ASD (indeed, recent studies suggest that diagnoses made as early as 14 months of age are reliable and stable [88,89]) and raise a number of important questions about early development in ASD that have broader implications for both clinical practice and the search for underlying neurobiological mechanisms.

When does ASD first manifest behaviorally? Both retrospective and prospective studies report consistent group differences in the domains listed above, differentiating children with ASD from TD comparison groups starting at 12–14 months. However, there remains considerable heterogeneity at an individual level; for example, Landa et al. [49,54] describe 'later-diagnosed' cases who are not detected as having developmental delays or social-communication deficits relative to non-ASD controls until 24 months. Conversely, is there evidence that behavioral indicators of ASD can be identified prior to 12 months? Several longitudinal studies of HR infants have failed to identify ASD-specific features at 6 months on any observational measure, coded live or from video [42,43,49,54]. Even at an individual level, Bryson et al. [45] described all 9 HR infants later diagnosed with ASD as demonstrating essentially typical social responsiveness, shared enjoyment and appropriate eye gaze at 6 months, with subsequent development of reduced social engagement, shared enjoyment and non-verbal communication by age 12–18 months. Some authors have reported subtle *group* differences between HR and LR infants at 6 months; for example, reduced spontaneous social orienting [46]; reduced social 'liveliness' during parent-child interaction [48] or passivity [43], but these features were observed in HR infants irrespective of ASD outcomes. Similarly, although persistent head lag was recently reported to predict ASD at 6 months in a cohort of 40 HR infants, the difference between children with ASD and those with other social communication delays at 30–36 months did not reach statistical significance [76]. One possible exception may be subtle abnormalities in postural symmetry, which were observed on home video in infants in lying position as early as the first 5 months of life [79], although this finding is based on a relatively small sample and no attempts at replication are yet available in the published literature.

One possibility is that the behavioral expression of vulnerability to ASD prior to 12 months is not restricted to infants who ultimately receive a diagnosis, but rather comprises a broader range of phenotypic features that become further differentiated over the course of development (an autism 'prodrome', as proposed by Yirmiya and Charman [90]). These features could include a particular temperamental profile (e.g., passivity, increased perceptual sensitivity [43,87,91]), subtle differences in social behavior (e.g., reduced spontaneous social orienting despite apparently typical responding to parental bids for attention; [46]), and non-specific developmental delays (e.g., in motor control; [76,82]). Indeed, Georgiades et al. [8] recently reported that even at 12 months, a subgroup could be identified among HR infants not diagnosed with ASD at age 3 who, nonetheless, had similar levels of symptoms at 12 months (as measured by the AOSI; [44]) as infants diagnosed with ASD. The critical question is what differentiates, from among a larger group of symptomatic infants, those on a developmental course toward ASD from those with other outcomes. There may be specific biological markers early in the first year of life (e.g., ERP profiles [53] or patterns of white matter connectivity from MRI [92]) that implicate brain abnormalities signifying higher risk of ASD. However, even such findings may reflect vulnerability rather than destiny, and there may be a host of as yet unidentified risk and resiliency factors that modify subsequent developmental course and outcomes. Some authors have suggested that ASD-specific differences early in infancy may not be apparent from general behavioral coding (e.g., during unstructured social interactions), but rather, may require a more in-depth assessment of social attention, using experimental methods such as eye-tracking. For example, Chawarska et al. [88] reported that 13–25-month olds with ASD demonstrate less attention to faces than typically developing controls while watching social scenes, but only when the adult in the video was actively cueing the child to engage socially, and proposed that such context-dependent differences in social attention may be critical to identifying ASD during infancy. Similarly, Rice et al. [93] proposed that atypical patterns of social attention to dynamic social scenes taken in natural settings (e.g., children playing), which have shown robust associations with levels of social impairment in preschool children with ASD, might be traced longitudinally to the earliest months of life. As yet, there are no published data demonstrating ASD-specific differences in social attention from eye-tracking studies involving infants younger than 12 months of age, but these methods show promise and may ultimately identify earlier markers (for a review, see Sasson and Elison [94]). That said, it is not surprising that manifestations of ASD, while potentially present in early infancy, would become more clearly differentiated from typical development and non-autistic delays over time. Other developmental disorders regarded as 'later-onset' relative to ASD also have behavioral manifestations during early infancy. For example, a recent meta-analysis of 22 longitudinal studies indicated that regulatory problem in the first year such as excessive crying, sleeping and/or feeding problems were statistically associated with risk of attention deficit hyperactivity disorder [95]. However, such problems are present in 20% of the general population, and are associated with only modest relative risk, so have limited utility to predict outcome on an individual basis.

Recent home video analyses of children with ASD as well as prospective studies of at-risk infants have also led to re-examination of the longstanding view that ASD onset generally follows one of two patterns: "early onset", in which symptoms are present from early infancy, and "regressive onset", when symptoms emerge following a period of essentially typical development and are associated with a frank loss in skills (e.g., in verbal abilities), frequently accompanied by reduced social interest and engagement

[96]. Regressive onset is reported to occur in 20–47% of children with ASD depending on case definition, and generally occurs in the second year of life, at a mean age of 19–21 months [97,98]. This classification is based primarily on retrospective parental reports, with additional corroborative evidence from home video analyses. For example, Werner and Dawson [36] found that children with ASD reported to have regressive onset did in fact show joint attention behaviors similar to typically developing children at 1 year, but by 2 years, these children had similar social communication impairments as children with ASD characterized as having early onset. However, both groups showed evidence of worsening social gaze over the course of the second year. More recently, Ozonoff et al. [37] adopted a more empirical approach to characterizing onset from home videos, identifying 3 latent classes described as 'early onset', 'regression' and 'plateau' based on frequency of social communication behaviors over multiple time points between ages 6 and 24 months. There was very little agreement between parent-reported onset and trajectory group assignment; moreover, the 'regression' trajectory was characterized by a steady decline and evidence of reduced social communication prior to 12 months of age [37], in contrast to the later and more discrete regression that parents generally describe. Findings from prospective research also diverge from the expectation of a dichotomous – that is, early versus regressive – onset classification [99]. Findings across longitudinal observational studies suggest that regression (i.e., overt skill loss) may be the extreme of a continuum of trajectories, characterized by developmental slowing or plateauing in language and non-verbal cognitive skills, as well as variable declines in social communication behavior [42–44,49,64]. Recent work by Landa et al. [64] suggests latent trajectory classes similar to those proposed by Ozonoff et al. in their home video analyses [37], although further research is needed to determine whether these classes will be associated with different long-term outcomes, and thus may have clinical utility for prognostic purposes.

Overall, there have been exciting advances in delineating early phenotypic expressions of ASD that can ultimately inform early detection and diagnosis, and create opportunities for earlier intervention. Although a comprehensive review of interventions for infants and toddlers diagnosed with ASD is beyond the scope of this paper, there are several well-defined treatment models shown in recent clinical trials to yield improvements in targeted skills (e.g., social-communication, imitation [100–102]) and global improvements in cognitive and adaptive function [4]. Further investigation of novel models of early ASD symptomatology (e.g., atypical regulation of attention and affect), and potential developmental cascade toward subsequent social communication impairment; [86,87]) may identify new targeted intervention, or conceivably, preventative strategies that can be implemented even earlier [3]. Recognizing that ASD occurs on a continuum, with variable manifestations and trajectories beginning in infancy (e.g., see Ozonoff et al. [42]), we would argue that targeting functional impairments as they emerge, even prior to the presence of a fully differentiated clinical diagnosis, offers the greatest hope to children and families. Thus, clinical trials of interventions targeting symptomatic infants 'at risk' remain a high priority.

While more systematic approaches (e.g., using experimental methods such as eye-tracking) and earlier characterization of behavioral symptoms should remain a major research priority, early risk prediction might be further enhanced through the incorporation of potential biomarkers. Promising findings from neuroelectrophysiology (see Elsabbagh et al., in this issue), and genetic research [103] may ultimately contribute to pre-symptomatic detection of at-risk infants, but much work remains to be done in assessing the potential sensitivity and specificity of such strategies in both high-risk and community samples. Further attention to effective application of early behavioral and biomarkers into community practice and related challenges in building health system capacity to ensure timely access to specialized diagnostic assessment and developmentally-appropriate evidence-based interventions is also needed to fully realize the promise of improved outcomes for the many children and families living with ASD.

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