Title: Regression in autism spectrum disorder: Reconciling findings from retrospective and prospective research

Running head: Regression in ASD – Reconciling Findings

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Lay Summary: Regression – a loss of previously established skills – occurs in a subset of children with ASD. Parental recall is not always accurate but studying younger siblings of children with ASD, 10-20% of whom will develop ASD, should make it possible to measure regression as it occurs. Clear-cut regression, like loss of language, has not often been reported in infant sibling studies, but recent research suggests that gradual loss of social engagement might be more common. This review looks at the evidence for regression from infant sibling studies and asks how study design affects the likelihood of capturing regression.

Abstract: The way in which the behavioural manifestations of Autism Spectrum Disorder (ASD) emerge in infancy is variable. Regression – loss of previously acquired skills – occurs in a subset of children. However, the aetiology and significance of regression remains unclear. Until recently, investigation of regression relied on retrospective report by parents or examination of home videos from early in life. However, home videos and retrospective report of the nature and timing of regression, and association with factors such as illness or immunisation, is potentially subject to bias. The advent of prospective studies of infant siblings at familial high-risk of ASD has the potential to document regression as it occurs. Recent research has suggested that subtle loss of skills occurs in a larger proportion of children with ASD than previously assumed; however, there are few reports of clear-cut regressions, such as that involving dramatic loss of language and other established skills, in the prospective literature. This could be because of the following: clear-cut regression occurs less commonly than parent report suggests, study design limits the potential to detect regression, or there are differences between multiplex and simplex families in the rate of de novo genetic mutations and therefore regression risk. This review will bring together literature from retrospective and prospective research and attempt to reconcile diverging findings, with a specific focus on methodological issues. Changing conceptualisations of regression will be discussed, as well as aetiological factors that may be associated with regression. The main challenges that need to be addressed to measure regression in prospective studies will be set out.

Key words: Autism Spectrum Disorder; Regression; Infant; High-risk siblings; Developmental trajectories

Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by persistent impairments in social interaction and communication, and the presence of restrictive and repetitive patterns of behaviour, interests and activities, and sensory anomalies (DSM-5, APA, 2013; ICD-10, WHO, 1993). The way in which ASD emerges in infancy is variable, with four onset patterns described: (i) emergence of symptoms in the first year of life, (ii) initial attainment of developmental milestones followed by a plateau in development, (iii) attainment of developmental milestones followed by a regression / loss of skills, and (iv) a mixed pattern of early delays followed by later loss (Ozonoff et al., 2008; Shumway et al., 2011; Goin-Kochel et al., 2015). These latter groups of children with regression will be the focus of this review.

Autism with regression describes a pattern whereby children lose skills that they have previously acquired. Recently there has been renewed interest in this group of children (Thurm et al., 2018). The recognition of marked heterogeneity in ASD has led to the search for subgroups in which determining aetiological factors might be more straightforward (Constantino & Charman, 2016). In addition, while studying regression has typically involved retrospective approaches that rely on home video-tapes and parental recall, more recent prospective longitudinal studies of infant siblings at high risk for ASD have enabled closer examination of early development in children with ASD (Jones et al., 2014; Szatmari et al., 2016). However, findings from retrospective and prospective studies have diverged widely (e.g., Hansen et al., 2008; Ozonoff et al., 2010), raising important questions as to the validity of regression as a distinct subgroup in ASD. For example, while regression is reported to occur within 20-30% of children with ASD by retrospective studies, clear-cut regressions have been rarely reported in prospective research (Rogers, 2009).

This review will bring together literature from retrospective and prospective approaches and explore discrepancies between them, discuss methodological issues that may lead to diverging findings, consider how concepts of regression are changing, and set out the main challenges that need to be addressed to measure regression in ASD. The literature involving retrospective study designs has been recently reviewed (Barger et al., 2013) and so greater emphasis will be placed on prospective studies and on integrating findings from retrospective and prospective approaches.

Defining regression

Regression in ASD is typically considered to involve loss of skills between 15 and 30 months of age, with a mean of 21 months (Barger et al., 2013). This is differentiated from the dramatic loss of skills seen in childhood disintegrative disorder (CDD; also known as Heller's syndrome). CDD involves rapid loss of skills across multiple domains between the ages of 2 and 10 years (Volkmar & Rutter, 1995; Matson & Mahon, 2009) after a prolonged period of typical development, and can include loss of

language, social skills, play, adaptive behaviour, bowel or bladder control, and motor skills. It is extremely rare, estimated to occur in 1.7 per 100,000 subjects (Fombonne, 2002) and no common aetiological factor has been identified. Furthermore, it is no longer included as a separate diagnostic entity in DSM-5. Given the low prevalence and lack of research about CDD, this review will focus primarily on regression as it more typically occurs in early development.

Regression in ASD has been defined in multiple ways and there is no agreed definition (Barger et al., 2013; Barger & Campbell, 2014). Most commonly measured are language regression (loss of spoken language) or language/social regression (loss of verbalisations and other social skills), although authors describe loss of other skills (such as motor skills), or use less clearly defined terms such as autistic regression, developmental regression, or cognitive regression that might encompass loss of verbal and/or nonverbal communication, sociability, play or cognition (e.g., Hrdlicka et al., 2004; Shattuck et al., 2009). Within these categories, there is variability in criteria for the level or duration of skills required before loss, the amount lost (e.g., the number of words), the duration of the loss, and the age by which loss must have occurred (for recent reviews see Barger et al., 2013 and Barger & Campbell, 2014).

The lack of a widely accepted operational definition of regression makes comparisons between studies difficult. Furthermore, these definitions have been developed with retrospective parental report methods and they may not map onto the various domains that can be measured using other methods. So while loss of words may be most salient to parents, more subtle losses of social communicative behaviours, for example, might be detectable in prospective studies but not captured by current definitions.

Evidence for Regression and Prevalence Rates

Retrospective Studies

The standardised parental interview, the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) is frequently used to document regression, requiring that skills be clearly established prior to a substantial loss. However, parents may have difficulties identifying and describing changing patterns of development; up to 45% do not report losses of social-communication behaviours, other than language, that have been empirically classified in home videos (Ozonoff et al., 2011a). Other forms of retrospective recall bias, such as reporting later age of language milestones and inflating symptom severity (Hus et al., 2011; Jones et al., 2015) also have the potential to limit accuracy of parental reports of regression. Similarly, while home videos provide evidence for the presence of social-communication behaviours early in life and subsequent decline,

findings may be constrained due to recording bias and lack of standardised data (Yirmiya & Charman, 2010; Ozonoff et al., 2011a).

A recent meta-analysis estimated overall prevalence of regression in ASD as 32%, although methodological factors influenced prevalence (Barger et al., 2013). The highest prevalence was found in parent surveys (41%) and clinically ascertained samples (34%), and the lowest in population studies (22%; see also Bradley et al., 2016). Regression is associated with earlier age of diagnosis (Shattuck et al., 2009; Daniels & Mandell, 2014), with specific diagnostic categories (27-52% with childhood autism (ICD-10)/autistic disorder (DSM-IV), 18-37% of children with broader ASD, 2-22% of children with Asperger's syndrome; Lingam et al., 2003; Kalb et al., 2010), and with intellectual disability (Bradley et al., 2016). Children with regression may be more likely to be presented and referred for assessment, resulting in these children being over-represented in clinically ascertained samples.

Prevalence rates also vary depending on the type of regression measured. When the types of skills lost are not specified or any instance of social and/or language loss is included then this results in the highest rates (38-39%), whereas lower rates are found with loss of mixed skills (e.g., language and adaptive functioning; 33%) or language loss specifically (25%) (Barger et al., 2013). Lower prevalence rates appear when using stricter criteria or that require participants to have clearly established a skill prior to loss (Fombonne & Chakrabarti, 2001). For instance, Goin-Kochel et al. (2014) analysed ADI-R data from 2,105 children, 89% of whom also had data from a supplement designed to measure additional and more subtle skill losses (loss of skills that had been established for one month and/or that had been lost for a period of one month [cf. three months in the ADI-R] and additional areas such as loss of babbling or alertness). Although 36.9% of participants had reports of a loss of skills, about a third did not reach ADI-R criteria for regression. Similarly, Kalb et al. (2010), in a study of 2,720 children with ASD, suggest that many of the children with reported regression had not fully developed language skills prior to the loss, and may have been excluded if more stringent criteria for regression had been used. Pickles et al. (2009) have suggested that processes underlying regression may begin for some children before skills become fully established, as several studies have described children showing difficulties prior to regression, such as regulatory symptoms (Werner & Dawson, 2005) or delayed acquisition of skills (Thurm et al., 2014). ADI-R criteria, which require that skills have been established and used on a daily basis for a minimum of three months prior to loss, could underestimate prevalence of regression. Alternatively, difficulty in discerning the nature of pre-loss skills via parent report could result in overestimation of regression, such as by including those children who lose only echolalic speech (Barbaresi, 2016). In this case

there may not be a true loss, but a failure to progress from early vocalisations to fully communicative speech (Klin et al., 2015).

In summary, retrospective studies may be biased by: (i) clinically ascertained samples, which may overestimate the prevalence of regression by incorporating a high proportion of more severely affected children; (ii) reliance on parental report measures, which may be limited by difficulty recalling more subtle losses or accurately describing the level of skills before loss; (iii) the use of strict criteria requiring skills to be fully established prior to loss. Given these limitations of retrospective studies, prospective approaches may seem to have greater potential to document regression as it unfolds.

Prospective Studies

In recent years the early development of children at risk for ASD has been studied using the infant sibling design (Jones et al., 2014; Szatmari et al., 2016). The sibling recurrence rate for ASD is around 10% in community samples (Constantino et al., 2010) and up to 20% in younger siblings of children with ASD (Ozonoff et al., 2011b; Messinger et al., 2015) compared to a population prevalence of 1-2% (Christensen et al., 2016), meaning younger siblings of children with ASD form a sample enriched for children at higher risk for ASD. By definition, younger siblings who develop ASD are from multiplex families and this could bias findings if the risk of regression differs between multiplex and simplex families. The rate of regression in multiplex families (23.9%; Parr et al., 2011) is not dissimilar to that reported from studies that did not select for multiplex families (e.g., 33%, Goldberg et al., 2003; 25% with loss of words, Lord et al., 2004). Cognitive profiles are broadly similar across probands from simplex and multiplex families, with subtle differences (greater impairment in simplex probands) only becoming apparent with within family comparisons between siblings (Oerlemans et al., 2016).

However, there is evidence that differences in risk factors exist, such as increased quantitative autistic traits in family members in multiplex families (Zwaigenbaum et al., 2007; Schwichtenberg et al., 2010), and increased numbers of de novo genetic mutations in patients with sporadic autism (Sebat et al., 2007). These differences may relate to risk of regression, as there are reports of regression occurring at relatively high rates in the context of genetic or metabolic syndromes. For example, loss of skills has been noted in 65% of a sample of individuals with Phelan-McDermid syndrome caused by SHANK3 point mutations (De Rubeis et al., 2018), 53% of boys with MECP2 duplication syndrome (Peters et al., 2013), and 61% of patients with ASD and mitochondrial disease (Shoffner et al., 2010). The expression profile of candidate genes for Childhood Disintegrative Disorder (CDD) resembles that of individuals from simplex families who have autism

with regression, but not that of individuals without regression (Gupta et al., 2017), suggesting that de novo genetic mutations may play a role in regression. Furthermore, Sacrey et al. (2017) found lower levels of ASD symptoms and a higher rate of females with ASD in an infant sibling sample compared to clinically ascertained children, which may represent either differences between multiplex and simplex families or under-recognition of girls and children with more subtle difficulties in the community. The inclusion of a greater proportion of less severely affected children could reduce the rate of regression observed in infant sibling studies. It seems possible that risk of regression is lower in multiplex families and that cases of clear-cut regression may be less likely to occur in infant sibling studies (Jones et al., 2014). These potential differences should be kept in mind when considering the emerging body of prospective data with relevance to regression in ASD.

Case Studies

Dawson et al. (2000) outlined the development of a younger sibling of a child with Asperger syndrome, who also developed ASD. This infant was referred for feeding problems and was assessed frequently between the ages of 2.5 and 24 months. There was a reduction in use of eye-contact, imitative games and imitative vocal responses, alongside cognitive decline from the 12th to 1st percentile based on standardised assessments (Bayley's Scales of Infant and Toddler Development [BSID] and Mullen Scales of Early Learning [MSEL]). Similarly, Klin et al. (2004) assessed a younger sibling of a child with autism at 15, 23 and 34 months. This child, who developed ASD, lost words between 12 and 15 months of age and this coincided with a decrease in social engagement. While the level of symptoms of ASD remained stable across assessments, progress in acquisition of adaptive skills was minimal, resulting in a drop in standard scores. It was not clear whether this represented regression or initial language acquisition that was not reinforced by a predisposition to seek communication with others and so faded away (Klin et al., 2004).

Bryson et al. (2007) followed nine high risk infant siblings between 6 and 36 months of age. All showed some loss of social-emotional connectedness over time, yet fell into two subgroups. Based on the BSID or MSEL, six children decreased from near average IQ to severe cognitive impairment between 12 and 24-36 months. Symptoms of ASD emerged or were more striking at an earlier age in this 'early onset' subgroup, than in the remaining three participants who continued to obtain average or near average IQ scores. However, the authors noted that the use of different cognitive measures made it unclear whether this reflected loss of skills or an arrest in cognitive development. Nevertheless, qualitative reports provide insight into the nature and timing of these changes, with some infants showing clearer loss of skills. For example, one child (Case 1) showed consistent eye contact, social anticipation to peek-a-boo, and social smiling at 6 months, yet by 12

months showed inconsistent eye contact, no social anticipation, and reduced social smiling. Another child (Case 4) lost expressive language at 19 months, losing around 10 words that had been used functionally, and at 24 months reached criteria for ASD. Expressive language began to return at 24 months, yet remained limited at 36 months. In both cases, regression was preceded by atypical development characteristic of ASD, such as impoverished visual fixation, and/or repetitive interests in particular objects, and/or cognitive or motor delay (Bryson et al., 2007; Rogers, 2009).

These early reports provided rich qualitative data on small numbers of siblings. Subsequently, a number of prospective studies have studied larger numbers of siblings and provide data that allows loss or decline in skills during the early years to be measured (see Table 1).

Infant Sibling Studies

A number of infant sibling studies have examined social and language domains where regression might be expected to occur. Landa et al. (2013) examined social, language and motor trajectories, in children with early onset ASD (by 14 months; n=28), later onset ASD (after 14 but before 36 months; n=26) and no ASD (n=181). Although groups demonstrated similar developmental levels at 6 months, ASD groups subsequently showed reduced frequency of shared positive affect, and developmental deceleration and plateau in language and communication. An earlier report of a partially overlapping sample also showed a decline in variety of gestures produced by children in the later ASD group (Landa et al., 2007). A minority of children showed evidence for language loss: 29% of early onset ASD, 19% of later onset ASD, and 2% of non-ASD children lost raw score points on both receptive and expressive language scales of the MSEL (Landa et al., 2013). Of the non-ASD children who lost language skills, four of five had language and/or social impairment at 36 months. Despite these language losses, parents did not report them during the ADI-R and the authors suggest that this might be because the losses were gradual. An earlier report of this study (Landa & Garrett-Mayer, 2006) included data from 87 infants, 24 of whom met criteria for ASD by 24 months. Of the infants with ASD, ten (42%) had MSEL raw scores on one or more scales that were lower at 24 months than at 14 months, eight of whom showed clinical worsening in social and communication functioning and eight lost raw score points in language domains. A further four infants with ASD had clinical regression in social and communication functioning but did not lose raw score points on the MSEL. Despite losses in some children, data at the group level showed gains over time, although trajectories were slower in the ASD versus non-ASD group. This highlights that group data may mask individuals who have lost skills.

Ozonoff et al. (2010) investigated changes in social, cognitive and language skills in infant siblings who developed ASD and low risk typically developing children. Behaviours measured

included gaze to faces, social smiles, directed vocalisations, an examiner rating of social engagement, and developmental quotient from the MSEL. Groups performed similarly on all measures at 6 months. However, infants subsequently diagnosed with ASD showed decreases in social communication behaviours over time. The frequency of gaze to faces decreased from levels comparable to typical infants at 6 months of age (~ 3/minute) to lower levels by 36 months of age (<1/minute). The rate remained consistent in typically developing infants. Examiner ratings of social engagement also suggested a decline over time in the ASD group, while remaining stable in typically developing infants. In contrast, social smiles and directed vocalisations did not decrease but failed to increase over time in the ASD group. There was no evidence of a decline in cognitive and language skills: MSEL raw scores in the ASD group increased over time, albeit at a slower rate than typically developing children. However, group data does not rule out the possibility that some children experienced loss; one parent reported loss of language during the ADI-R. To explore individual trajectories, the authors calculated decline in gaze to faces greater than the 95% confidence interval for visit-to-visit change in the typically developing group. They found that 86.4% of infants with ASD showed declines outside of this range, suggesting prevalence of regression markedly higher than that documented using retrospective methods. The majority of parents did not report a loss of skills when interviewed using the ADI-R, suggesting that it did not capture slow losses in social engagement. The authors conclude that specific social communication behaviours clearly decrease in infants with ASD, rather than failing to progress. Moreover, these declines were often followed by a failure to progress in other developmental domains.

In a further, larger study (n=32 ASD, n=117 high risk non-ASD, and n=81 low risk non-ASD siblings), Ozonoff et al. (2018) measured regression using four different measures to look at the effect of informant (examiner vs. parent), decision type (categorical vs. dimensional), and timing of assessment (retrospective vs. prospective) on classification of regression. Using prospective, dimensional measures of social engagement, there was decline in the ASD group from a level comparable to non-ASD groups at 6 months of age to be significantly lower by 12 months, with continuing decline through 24-36 months. Within the ASD group 88% were classified as showing regression using examiner ratings and 69% using parent ratings. When parents were asked to make a categorical judgement about whether their child had shown decreases in skills between study visits, 47% reported regression. Finally, when asked to make a retrospective categorical judgement using the ADI-R, only 29% reported regression. The authors suggest that while parents are able to implicitly identify changes when rating current behaviours over time, they were less likely to label this as a loss when forced to make a categorical judgement. Further evidence for a decline in social behaviour was described by Miller et al. (2017), who found that fifty-four percent of infant siblings

with ASD who oriented to their name during assessment at 12 months of age failed to respond during a subsequent assessment between 15 and 24 months. However, 30% of infants without ASD also failed to respond during at least one other assessment, suggesting that orienting to name, at least in the context of formal assessment, may not be stable during early development. Temperament has also been studied in infant siblings. A prospective study of 54 high risk infant siblings showed that infants later diagnosed with ASD show a decrease in adaptability and approach behaviour between 6 and 36 months of age, despite showing greater adaptability and approach than infants without ASD at 6-12 months (Rosario et al., 2014).

The infant sibling studies described above suggest definite loss of language or social communication as measured by the MSEL in 19-42% of infants with ASD, rates broadly consistent with those reported using retrospective methods (Barger et al., 2013). Furthermore, gradual loss of social engagement seems to occur in the majority of infant siblings with ASD, and is not necessarily reported during the ADI-R.

Beyond infant siblings studies, evidence for loss of language and social communication has been found in a general population study of infants subsequently classified as ASD, language impairment (LI), or typically developing (TD) (Brignell et al., 2017). Using the Communication Symbolic Behaviour Scales Developmental Profile – Infant Toddler Checklist (CSBS-ITC) and the MacArthur-Bates Communicative Development Inventories (CDI), raw scores were compared at 12 and 24 months. Only two children (one ASD, one LI) lost expressive vocabulary on the CDI, though detection of loss was limited by the small number of words typically used by infants at 12 months, resulting in a an extremely conservative measure of loss. On the CSBS DP, 41% of infants with ASD, 30% of LI infants, and 26% of TD infants had lower scores at 24 months than 12 months on at least one cluster of social communication skills, most commonly ‘emotion and use of eye gaze’. Whereas in the majority of LI and TD infants loss was restricted to one domain, infants with ASD were more likely to have pervasive loss across two or more domains. Limitations include reliance on parent-report, only two time points, and the relatively long gap between assessments. Loss on the CSBS-ITC, a parent-report checklist, included ratings that went from ‘always’ to ‘sometimes’ using a skill; caution is warranted in interpreting this as regression, especially in those with lower scores in only one domain, as this may reflect short-term fluctuations in (parents’ perceptions of) social and communication behaviour rather than loss of skills.

It is possible that infants with ASD lose skills in areas that are difficult to detect with standard observational or parent-report measures, and a small number of studies have looked at visual attention measured using laboratory administered tasks in younger infants. Jones and Klin

(2013) examined high risk infant siblings and low risk controls on gaze response to videos of natural caregiver interactions. While infants without ASD demonstrated an increasing tendency to fixate on eyes over the first two years of life, siblings with subthreshold symptoms showed neither increasing nor decreasing eye fixation, and infants later diagnosed with ASD showed declining eye fixation. Eye fixation did not differ between groups at 2 months and there was marked variation between individuals within each group, yet the majority of children (10/11) who subsequently developed ASD had a declining trajectory. Some caution is warranted due to the small sample size and relatively small decline in eye gaze during the first 6 months (Brock, 2013). However, these results are broadly consistent with declining gaze to faces in 86% of infants diagnosed with ASD reported by Ozonoff et al. (2010).

Zwaigenbaum et al. (2005) used a computerized Visual Orienting (Disengage) Task at age 6 and 12 months in 20 infant siblings. This task measures the latency to disengage from an initial visual stimulus to shift attention to a competing stimulus at the periphery of the screen. No significant group differences were observed at 6 or 12 months of age. However, a subset of high-risk siblings (25%) showed longer latencies at 12 than 6 months of age. Each of the infants who declined in ability to disengage attention met ADOS criteria for ASD at 24 months of age. No infant whose performance was similar or better at 12 months met criteria for ASD. A further report from the same cohort demonstrated that increasing latency to disengage was specific to shifting attention to the left hand side, suggesting right hemisphere dysfunction (Bryson et al., 2017). Visual attention during naturalistic play was reported for a subset of these siblings but interpretation was limited by the reporting of group data only (Sacrey et al., 2013).

Elsabbagh et al. (2013) similarly measured attentional disengagement using a gap-overlap task in children subsequently classified at 36 months as ASD, other developmental concerns, or typically developing. While there was no difference between groups at 7 months, by 14 months the ASD group showed longer latency to disengage attention compared to the other high risk groups and low risk controls. At the group level, typically developing infants and those high risk infants later classified with other developmental concerns showed faster attentional shifts with age, whereas similar gains in performance were not seen for the high-risk group with ASD. Individual data showed that of those infants with ASD, 40% had a longer latency to disengage at 14 months than they did at 7 months, showing a decrement in performance. This may differ from Zwaigenbaum et al. (2005), where *all* of those who subsequently met ASD criteria showed a decrement in performance, because of differences in diagnostic classification. Whereas Zwaigenbaum et al. (2005) used ADOS criteria at 24 months, Elsabbagh et al. (2013) classified children at 36 months using ADOS, ADI-R, and ICD-10

criteria, potentially including children who would not have met ADOS criteria at 24 months. This suggests that for at least a subset of infants with ASD there is a decline in their ability to make attentional shifts, whereas others show a plateau in the development of visual orienting. This is not a domain typically considered under the umbrella of regression, and may not be reported by parents, yet may represent a decline in performance that was previously comparable to typically developing infants. However, a proportion of infants who develop ASD would be expected to develop co-occurring ADHD symptoms and the relationship between early emerging attentional difficulties, ASD and ADHD risk is unclear. For example, attenuated reduction in looks to faces between 9 and 15 months of age was associated with poorer effortful control at 36 months, though not with symptoms of ASD or ADHD (Hendry et al., 2018). Decreasing performance on an inhibition task between 12 and 24 months of age has been demonstrated in high risk infant siblings, though this was regardless of subsequent ASD status (St. John et al., 2016).

Taken as a whole, these findings suggest that between 6 and 14 months a substantial proportion of infants who later develop ASD experience increasing difficulties in disengaging visual attention (Zwaigenbaum et al., 2005; Elsabbagh et al., 2013) and the majority show declining fixation of eyes, gaze to faces, and social engagement, from typical levels in early infancy (2-6 months) to significantly reduced levels by 24-36 months (Ozonoff et al., 2010; Jones & Klin, 2013; Ozonoff et al., 2018). This may influence subsequent development as from 12 months onwards, children with ASD show slower trajectories of cognitive and language development relative to comparison groups. Loss of language has been reported at rates of 19-29% (Landa et al., 2013), similar to that reported in retrospective studies using population samples (Barger et al., 2013). Figure 1 summarizes this by superimposing key findings for visual attention, eye fixation, social engagement, and language development and loss.

A number of prospective studies have reported data that make it more challenging to determine if regression has occurred. These include studies in which only standardised scores (Landa et al., 2012; Lord et al., 2012; Estes et al., 2015; Levin et al., 2017) or group data are reported (Barbaro & Dissanayake, 2012; Ibañez et al., 2013; Filliter et al., 2015; Gliga et al., 2015; Caravella & Roberts, 2017; Chenausky et al., 2017; Iverson et al., 2018), where loss and plateau are not differentiated (Brian et al., 2014), or where longitudinal analysis was not carried out (Bedford, et al., 2012; Gangi et al., 2017). While these studies show progressive divergence from typical development, they cannot differentiate developmental arrest or slowing from regression, and group data may have obscured variability within groups (Elsabbagh & Johnson, 2010). Individual data shows variation within groups and over time (see, for example Venker et al., 2014), consistent with

the qualitative descriptions by Bryson et al. (2007) which suggest that patterns of development may fluctuate, demonstrating both losses and gains between points of assessment. This may not be detectable in studies in which the intervals between assessments are relatively long (e.g., Brignell et al., 2017).

The studies above highlight a number of important methodological issues. First, some studies have reported results using standardized, age-normed scores. A decline in standard scores can result from a failure to gain skills or a loss of previously acquired skills, resulting in inconclusive evidence of loss. Second, some studies report only group data and this may mask individuals that experience a loss of skills. Third, the interval between assessments may be too long to identify skills that have been lost and subsequently regained. Fourth, the types of skills measured and methods of measurement vary between studies, making direct comparison challenging. Fifth, the families included in prospective infant sibling studies may not be typical of all families affected by ASD. While current evidence from prospective studies is limited by these issues, the integration of retrospective and prospective methods has the potential to help further develop the concept of regression.

Refining the concept of regression

Both retrospective and prospective approaches are necessary to refine the concept of regression. Thurm et al. (2014) noted that retrospective research expanded on the categories of early onset and regressive autism by identifying patterns of mixed onset whereby children demonstrate early delays prior to the onset of regression (Ozonoff et al., 2005; Ozonoff et al., 2008). While regression is frequently reported in infants already demonstrating subtle delays (Rogers, 2004), other retrospective studies (Lord et al., 2004; Werner & Dawson, 2005; Baird et al., 2008) have suggested that groups experiencing regression display higher levels of social and language development in the first year of life than counterparts without regression (Barger et al., 2013). Some prospective studies have reported tentative evidence in support of this, with trends towards greater eye fixations at 2 months (Jones & Klin, 2013; though see criticism by Brock, 2013), more frequent gaze to faces at 6 months (Ozonoff et al., 2010), and greater adaptability and approach behaviour (Rosario et al., 2014) in infants with ASD compared to typical infants, prior to a decline.

The relationship between the early, subtle losses shown by a majority of children with ASD in some prospective studies – decline in gaze to faces, eye fixation, and social engagement (Ozonoff et al., 2010; Jones & Klin, 2013; Ozonoff et al., 2018) and decreasing ability to disengage visual attention (Zwaigenbaum et al., 2005; Elsabbagh et al., 2013) – and the more overt losses described by parents is unclear. Early automatic orienting behaviour may be driven by subcortical mechanisms, with control shifting to cortical mechanisms during the first year of life (Johnson, 2005; Jones et al.,

2014). Apparent losses may therefore result from a failure of cortical mechanisms to develop when subcortical mechanisms are in decline (Klin et al., 2015). The fact that loss in social orienting, shared positive affect, and attentional disengagement seem to occur over roughly the same timescale (Figure 1) is suggestive of a common mechanism such as atypical top-down modulation of perceptual input (Jones et al., 2014). Furthermore, some cases of apparent language loss could be loss of echolalic speech (Barbaresi, 2016) and represent failure to progress from early vocalisations to fully communicative speech (Klin et al., 2015), and could therefore be on a continuum with earlier losses. If similar mechanisms underlie both early and later social attention and engagement, then a broader concept of regression may be required to include gradual social withdrawal and loss of social engagement in toddlers (Ozonoff et al., 2010; Lord et al., 2012). Defined in this way, ASD onset may be better considered as a continuum characterised by the amount and timing of regression, ranging from early and gradual loss that is difficult to quantify, through to later loss of clearly established skills that appears more dramatic (Ozonoff et al., 2010). In this model, the form regression takes may reflect the timing in relation to the trajectory of skill development, such that very early regression would affect social engagement but regression in the second year of life would be more likely to affect communication and play skills. However, it is possible that loss of clearly established language and other skills in the second year or life or later are conceptually and mechanistically distinct from early gradual losses; if the risks differ in multiplex and simplex families then infant sibling studies may not be able to address this question.

The observation from prospective research that some infants have fluctuating patterns of losses and gains (Bryson et al., 2007) highlights the difficulty of handling parent-reported losses that do not meet ADI-R criteria for regression (Thurm et al., 2014). These children may not be included in regression groups; meanwhile, regression groups can include children with widely varying pre-loss skill attainment (Ozonoff et al., 2008; Thurm et al., 2014). To address this, Thurm et al. (2014) used caregiver interviews to examine attainment and loss of skills in the first four years of life in children with autism, PDD-NOS, non-spectrum developmental delays and typically development. Data on timing was also reported, capturing age-delineated skill attainment and loss, and both gradual subtle losses and more abrupt cases of regression. Loss was highest in those with autism (63%), followed by PDD-NOS (60%), DD (24%) and TD (3%). While loss of at least one skill was reported in the majority of ASD participants, loss of skills is not universal, nor unique to ASD. The processes whereby symptoms of ASD unfold, with early delays in social-communication in children developing ASD, alongside a loss of at least one skill in the majority of these participants, may not be consistent with a categorical approach to regression. Thurm et al. (2014) propose that it may be more useful to model onset dimensionally and conceptualise regression as a continuum that starts with varying

degrees of early delays in the attainment of social communication skills, followed by varying degrees of loss of skills. Alternatively, onset may be better characterised by pervasive early loss of social engagement, followed by failure to gain social communication skills in the second year, with loss of language in a sizeable minority of children (Ozonoff et al., 2010; Landa et al., 2013; Ozonoff et al., 2018). Capturing the dimensional nature of loss and recovery of skills might be important in elucidating individual differences in compensatory capacity to rectify regression. Exploring these issues will be necessary in future prospective studies.

Association with aetiological factors

A number of studies have examined the association between regression and putative aetiological factors. However, these have mostly relied on retrospective parent report of regression and, given the limitations inherent in retrospective report, this is likely to limit the conclusions that can be drawn. With this caveat in mind, research examining factors potentially associated with regression will be briefly reviewed. Based on current evidence, there is little reason to believe that ASD with regression represents a separate condition (Brewer, 2014). A large study of multiplex families with ASD showed that the concordance rate for regression in affected sibling pairs was not elevated above that expected by chance, suggesting that there is not a familial influence on regression over and above the influence on ASD itself (Parr et al. 2011). Similarly, the suggestion that autistic regression with gastrointestinal problems had arisen as a distinct phenotype associated with the MMR immunisation has not been supported by evidence (Fombonne & Chakrabarti, 2001; Lingam et al., 2003). There is also no evidence that the rate of regression differs between males and females (Barger et al., 2013). ASD with regression may not exist as a distinct subtype in terms of aetiology. However, it is possible that additive or multiplicative effects of multiple genetic or environmental risk factors contribute to variable trajectories in the onset of ASD, including regression (Gliga et al., 2014).

There is evidence that epilepsy is associated with regression in ASD, though effect sizes are small and inconsistent methodology and definitions, of both regression and epilepsy, limit interpretation (Hrdlicka et al., 2004; Oslejskova et al., 2008; Besag & Blackmon, 2014; Barger et al., 2017; Gadow et al., 2017; Jack & Pelphrey, 2017). However, specific seizure types may increase risk of regression and this may be more apparent using a prospective approach. Humphrey et al. (2014), using a prospective design, followed 11 infants with the genetic disorder tuberous sclerosis complex (TSC) aged under 3 years, in which 6 developed epileptic spasms and 5 developed other forms of seizures. Those developing spasms showed a clear decline in IQ scores, whereas there was no decline in those developing other seizure types. This represented a plateau rather than loss of

language or cognitive skills (there was no loss of raw score points on the MSEL). However, case studies reported loss of social, communication and play skills in children with TSC following the onset of infantile spasms (Humphrey et al., 2006; Srivastava & Bolton, 2013). To what extent these findings are applicable to infants with other genetic disorders or idiopathic ASD remains to be explored.

Autoimmunity and neuroinflammation have been associated with regression, such as a higher rate of autoimmune disease in family members of children with ADI-R reported regression compared to children without regression (Scott et al., 2017). Children with a clinical diagnosis of regressive autism have been shown to have subtle differences in humeral and cellular immunity when compared with typically developing children, possibly reflecting inflammatory, allergic or autoimmune conditions (Wasilewska et al., 2012). Anti-brain auto-antibodies have been associated with Landau-Kleffner syndrome variant (regression associated with abnormal electroencephalogram), albeit in a small sample (Connolly et al., 1999). Reports of improvement after treatment of children with ASD with immune modulating drugs is suggestive of the role of immune factors in the aetiology of regression in ASD; however, the literature is limited to pilot and case studies, precluding firm conclusions (Chez & Guide-Estrada, 2010).

Brain volume and rate of head circumference growth has been explored in relation to ADI-R defined regression in recent studies. In a sample of 114 2-4 year-old children with ASD (61 with regression) and 66 typically developing (TD) controls, Nordahl et al. (2011) measured brain volume using MRI and used repeated head circumference measurements as an indicator of brain growth from birth to 18 months. Children with regression were more likely to have greater cerebral volume and 22% had megalencephaly (greater than 2 SD above the mean of the TD control group), compared to 5% of the non-regressive ASD group. Increase in head circumference was apparent from 4-6 months of age and was specific to boys. The authors suggest that other aspects of brain structure or function, such as white matter microstructure and connectivity, should also be explored. In contrast, Webb et al. (2007) did not find an association between rate of head circumference growth and ASD onset pattern, though the sample size was smaller (n=28).

Thomas et al. (2016) proposed that regression and other onset trajectories could be explained through a mechanism of over-pruning of synaptic connections early in development. Computer simulations were used to model the pruning of excess connectivity, while manipulating the threshold at which pruning would occur, postulating that raising the threshold so that stronger connections would be pruned might reflect a risk factor predisposing to ASD. Other parameters such as the pruning rate were allowed to vary, leading to individual differences within the population. This demonstrated that a single pathological mechanism in the context of individual differences in

other factors could result in developmental trajectories that corresponded to early-onset, late-onset, and regression in a simulated cognitive domain.

Delineating the similarities and differences between regression in idiopathic ASD and in specific disorders, such as Childhood Disintegrative Disorder (Volkmar & Rutter, 1995; Matson & Mahon, 2009) and Landau-Kleffner syndrome (acquired epileptic aphasia of childhood; Robinson et al., 2001) may suggest mechanisms that could underlie regression at different stages of development (Jack & Pelphrey, 2017). Furthermore, loss of skills beyond infancy – such as catatonic symptoms in adolescence or adulthood – may occur at higher rates than previously thought (Breen & Hare, 2017). While research is limited, further research into the similarities and differences between loss of skills in infancy and adolescence or adulthood is warranted and may suggest directions for investigation of aetiology such as auto-immunity (Kiani et al, 2015) and genetic factors (Breckpot et al, 2016), as well as possible treatments (Dhossche, 2014). Importantly, attempts to explore aetiology should move beyond retrospective parent-report of regression, utilising prospective designs and considering dimensional definitions of regression alongside categorical approaches.

Clinical implications

Findings that a significant proportion of children who develop ASD show a decline in developmental abilities in infancy indicates a need for early identification, regular monitoring and standardised assessment of young children suspected of ASD, with careful follow up that continues beyond 12 and 18 month screens (Lord et al., 2012). As prospective studies more fully elucidate the way in which early developing skills are lost there will be a need to update tools that are used in clinical settings. In particular, the ADI-R used alone is likely to be insufficient and will provide a conservative measure of loss of skills. Alternative approaches, such as more detailed interviews, and repeated use of parent report checklists of current behaviour and health professionals' ratings of social communication and engagement during routine visits to track changes over time may provide more sensitive measures of regression (Ozonoff et al., 2010; Ozonoff et al., 2018). Collecting repeated data from large nationally representative samples of infants without ASD could allow the construction of growth charts, similar to the CDC Growth Charts and WHO Child Growth Standards that are used to track indicators of physical development such as weight, height, and head circumference (Kuczmarski, et al., 2002; WHO, 2018). Using growth charts with smoothed percentile curves for key indicators – for example, social engagement, language, and head circumference – may make it possible to detect infants whose trajectory of development deviates from the norm, even when

losses are subtle. Figure 2 shows what this could look like for ratings of social engagement as presented by Ozonoff et al. (2018).

The wide variability in developmental trajectories of infants at risk of ASD is likely to be influenced by dynamic interactions between genetic and environmental risk factors, such that early atypical trajectories can be compounded or restored to a more typical trajectory during early development (Elsabbagh & Johnson, 2010). Careful documentation of recovery following regression with elaboration on the level of support received by the infant, such as parental prompts or structured interventions, may help to identify risk and protective factors (Elsabbagh & Johnson, 2007). This could allow measurement of the effectiveness of behavioural interventions in comparison to the natural unfolding of the developmental process (Zwaigenbaum et al., 2007), in line with the resiliency framework (Szatmari, 2017). Equally, if it were possible to identify early losses as they begin to occur, this may have practical implications such as targeting interventions to limit the loss. For example, if it were possible to detect early decreases in social engagement and attentional disengagement in children for whom there are developmental concerns or who are at risk through having a sibling with ASD, this might identify those who may benefit from intervention designed to be delivered during the prodrome of ASD (e.g., Green et al, 2017).

Challenges for Future Research

There are a number of methodological issues in both retrospective and prospective studies that limit current understanding of regression and that should be addressed in future research.

Definition

Firstly, it is essential to reach consensus regarding a definition of regression to enable consistency across studies. Current definitions, developed with retrospective parental report approaches, may need to be broadened to include skills that were not fully established prior to loss, fluctuating patterns of losses and gains, and subtle losses in aspects of social engagement and early developing skills that are harder to capture using parental report but that might be detected using experimental tasks (e.g., gaze to faces, attentional disengagement). New definitions should combine a dimensional with a categorical approach. This could involve modelling developmental trajectories in typically developing infants, taking into account variability in skills over time and measurement error, to make it possible to determine when infants deviate from a typical trajectory. Ozonoff et al. (2010) used 95% confidence intervals for visit-to-visit change in the TD group in order to identify infants who showed decline that fell outside of this range; similar approaches to using developmental trajectories or normative modelling that quantifies normal variation have been proposed as ways to capture

deviation from normal trajectories (Thomas et al., 2009; Marquand et al., 2016) and may provide useful models for regression.

Retrospective tools

Advancing understanding of regression through prospective research should guide the development of retrospective methods. For instance, there is a need to build on measures such as the ADI-R to be able to capture losses that do not meet the current criteria for regression, and also better quantify pre-loss skills. As regression appears to be most frequently reported within the social-communication domain (Ozonoff et al., 2010), additional probes could be included to enable elaboration about social engagement, such as changes in direct gaze, orienting to name, spontaneous imitation or response to social overtures (Goldberg et al., 2003).

It may be helpful to utilise detailed record forms during assessments. For example, Goldberg et al. (2003) developed a Regression Supplement Form for use alongside the ADI-R. Routine inclusion of such methods could improve understanding of different patterns of regression (subtle, dramatic, fluctuating), timing of the onset, domains in which skills were lost, and identification of concurrent events or behavioural abnormalities observed prior to or following the loss. Similarly, Thurm et al. (2014) used the Regression Validation Interview alongside the ADI-R to investigate attainment and loss of skills. This interview included questions to assess pre-speech behaviours, communicative gestures and vocabulary, while recording data on timing, allowing developmental processes to be explored more fully.

Despite the limitations of the ADI-R in measuring regression, the fact that it is used consistently across studies means that it will remain a key source of information. When data is being pooled across studies and research sites it is essential that individual ADI-R items, and not just domain scores, are included in datasets. Furthermore, it is important to use the ADI-R, and not just the ADOS, at three year follow up in prospective studies if regression is to be consistently recorded.

Prospective methods

A key problem in prospective research has been the use of standardised measures of development that do not differentiate loss of skills from failure to progress or slowing in rate of development. Measurement that makes it possible to determine whether skills have been lost, including reporting raw scores, is essential. Furthermore, children must be assessed frequently enough so as not to miss loss of skills that are subsequently regained. A combination of frequent naturalistic observations, vocabulary checklists, or parent diaries, with less frequent standardised assessments at key landmarks may provide the best balance between acquiring rich data on early developmental

trajectory while reducing the cost and burden to families (Zwaigenbaum et al., 2007). The use of supplemental interviews to measure loss of skills would help to fully capture fluctuating patterns of gains and losses between visits (Goldberg et al., 2003; Thurm et al., 2014).

Reporting individual trajectories, rather than only group data, will be essential so as not to miss cases in which loss of skills has occurred. Likewise, researchers must consider how different measurement tools may influence interpretation of regression. For example, in depth measurement of social-communication behaviours may show a decline in a large proportion of infants with ASD. By comparison, loss of cognitive and language skills appears to be less frequently reported, particularly when assessed by standardised developmental tests. Measures such as the MSEL may not be sensitive to the type of losses seen in the onset of autism (Ozonoff et al., 2010). It is also necessary to consider how losses in different domains might be related to each other. Longitudinal measurement of multiple domains – from experimentally measured behaviours such as gaze patterns and attentional disengagement, to social communication behaviours, language and cognitive skills, and temperament – in the same individuals will be necessary to explore the dynamic relationships between them. This will help establish whether all infants with ASD lose some skills, but at different points in development, or whether only some infants lose skills but across multiple domains.

Longer term follow up will also be important to establish if different degrees of regression are associated with differences in autistic symptoms, cognitive profiles, or patterns of comorbidities during later childhood and adolescence. For example, ongoing prospective studies have reported a significant increase in the number of high-risk siblings identified with the broader autism phenotype and later-diagnosed ASD at age 7, compared to studies that have classified children at earlier stages of development (Miller et al., 2016; Shephard et al., 2017). It will be necessary to follow up children beyond the age of 3 to determine if early loss of skills is predictive of later emerging problems.

Long term study of high risk siblings could also help to clarify to what extent loss of skills features at later stages in development. Regression can occur at later ages in specific disorders, such as Childhood Disintegrative Disorder or Landau-Kleffner syndrome. It may be possible that unidentified gradual losses also occur in older children with idiopathic ASD, manifesting instead in the onset of catatonia or emotional or behavioural comorbidities. Documenting the reasons for referrals of older children with ASD may help establish whether regression is a factor in the development of associated problems.

Regression in specific disorders

ASD and regression occur in a number of specific disorders. While children with genetic disorders are often excluded from studies, a specific focus on regression in other disorders may help to elucidate underlying mechanisms that could have relevance in idiopathic ASD. For example, loss of cognitive, social communication, and play skills following infantile spasms in children with tuberous sclerosis complex (Humphrey et al., 2014) suggests that subtypes of epilepsy have either a causal role or act as a marker of other neural abnormalities. Neuroimaging or neurogenetic studies in children with specific disorders such as TSC, CDD, or Rett Syndrome (Gupta et al., 2017; Thurm et al., 2018) might reveal genetic and neural correlates that could suggest possible causal mechanisms for regression in idiopathic ASD.

Consistent documentation of comorbid disorders associated with regression including genetic conditions such as TSC, seizure disorders (including Landau-Kleffner Syndrome), and metabolic conditions, could provide direction for future research (Williams et al., 2015). Medical and neurodevelopmental comorbidities have been reported in children with regression and specific language impairments and developmental delays (encephalitis, Down's syndrome with leukaemia, stroke and epilepsy; Pickles et al., 2009; Thurm et al., 2014; Williams et al., 2015) and in children with ASD and 'fluctuating speech loss' (e.g. TSC, Fragile X; Lord et al., 2004). Such findings raise the question of how exclusion of children with specific medical conditions may influence understanding of regression (Zwaigenbaum et al., 2007).

Conclusions

Prospective research indicates that a subtle loss of skills may be observed more frequently in children with ASD than previously recognised. However, methodological limitations sometimes make it difficult to determine to what extent children have lost skills rather than showing a developmental plateau or slow gain of skills. A combination of retrospective parental report with a focus on gain and loss of skills, and prospective measurement of behaviours in a way that can differentiate regression from other trajectories will be necessary. A broadening of the domains in which loss of skills is measured will help to develop the concept of regression beyond the relatively narrow definitions employed in retrospective research. Given that retrospective reporting of regression may detect only the most dramatic loss of skills, it is likely that regression has been under-reported in much research to date. Improved definitions and measurement of regression will be essential for research that seeks to establish the prevalence of loss of skills or explore aetiological factors associated with regression. New approaches to tracking early development, such as the

development of standardised growth curves for early social development, may help with early identification and monitoring of infants who show early but gradual loss of social engagement.

Finally, it is still not clear how early and gradual losses are related to more dramatic regression involving loss of clearly established skills. It is possible that the latter occurs more commonly in children from simplex families where there is a greater risk of de novo genetic mutations; if this is the case, then prospective research utilising approaches other than the infant sibling design will be necessary to elucidate the full range of ways in which regression can manifest.

References

APA. (2013). Diagnostic and Statistical Manual of Mental Disorders (5th ed. ed.). Washington, DC.: American Psychiatric Association.

Baird, G., Charman, T., Pickles, A., Chandler, S., Loucas, T., Meldrum, D., Carcani-Rathwell, I., Serkana, D., Simonoff, E. (2008). Regression, Developmental Trajectory and Associated Problems in Disorders in the Autism Spectrum: The SNAP Study. Journal of Autism & Developmental Disorders, 38, 1827–1836, doi: 10.1007/s10803-008-0571-9

Barbaresi, W.J. (2016). The Meaning of "Regression" in Children with Autism Spectrum Disorder: Why Does It Matter? Journal of Developmental & Behavioral Pediatrics, 37, 506– 507.

Barbaro, J., & Dissanayake, C. (2012). Developmental profiles of infants and toddlers with autism spectrum disorders identified prospectively in a community-based setting. Journal of Autism & Developmental Disorders, 42:9, 1939-1948. doi: 10.1007/s10803-012-1441-z

Barger, B. D., & Campbell, J. M. (2014). Developmental Regression in Autism Spectrum Disorders: Implications for Clinical Outcomes. In V. B. Patel, V. R. Preedy & C. R. Martin (Eds.), Comprehensive Guide to Autism (pp. 1473-1493). New York: Springer

Barger, B. D., Campbell, J. M., & McDonough, J. D. (2013). Prevalence and onset of regression within autism spectrum disorders: a meta-analytic review. Journal of Autism & Developmental Disorders, 43:4, 817-828. doi: 10.1007/s10803-012-1621-x

Barger, B.D., Campbell, J., & Simmons, C. (2017). The relationship between regression in autism spectrum disorder, epilepsy, and atypical epileptiform EEGs: A meta-analytic review. Journal of Intellectual & Developmental Disability, 42:1, 45-60, doi:10.3109/13668250.2016.1208812

Bedford, R., Elsabbagh, M., Gliga, T., Pickles, A., Senju, A., Charman, T., Johnson, M.H., the BASIS team (2012). Precursors to Social and Communication Difficulties in Infants At-Risk for Autism: Gaze Following and Attentional Engagement. Journal Autism Developmental Disorders, 42, 2208–2218. doi: 10.1007/s10803-012-1450-y

Besag, F.M.C., Blackmon, K. (2014). Comments on Hughes JR. A review of recent reports on autism: 1000 studies published in 2007. Epilepsy & Behavior 2008;13:425– 437 and Hughes JR. Update on autism: A review of 1300 reports published in 2008. Epilepsy & Behavior 2009;16:569– 589. Epilepsy & Behavior, 40, 37–41. doi: http://dx.doi.org/10.1016/j.yebeh.2014.10.007

Bradley, C.C., Boan, A.D., Cohen, A.P., Charles, J.M., Carpenter, L.A. (2016). Reported History of Developmental Regression and Restricted, Repetitive Behaviors in Children with Autism Spectrum Disorders. Journal of Developmental & Behavioral Pediatrics, 37, 451–456.

Breckpot, J., Vercruyssen, M., Weyts, E., Vandevoort, S., D'Haenens, G., Van Buggenhout, G., Leempoels, L., Brischoux-Boucher, E., Van Maldergem, L., Renieri, A., Mencarelli, M.A., D'Angelo, C., Mericq, V., Hoffer, M.J., Tauber, M., Molinas, C., Castiglioni, C., Brison, N., Vermeesch, J.R., Danckaerts, M., Sienaert, P., Devriendt, K., Vogels, A. (2016). Copy number variation analysis in adults with catatonia confirms haploinsufficiency of SHANK3 as a predisposing factor. European Journal of Medical Genetics, 59:9, 436-443. doi: 10.1016/j.ejmg.2016.08.003

Breen, J., Hare, D. J. (2017). The nature and prevalence of catatonic symptoms in young people with autism. Journal of Intellectual Disability Research, 61:6, 580–593. doi: 10.1111/jir.12362

Brewer, R. L. (2014). Regressive Autism: A Study In Early Developmental Patterns. (Master of Science Master of Science), Southern Illinois University Carbondale. Retrieved from http://opensiuc.lib.siu.edu/gs_rp/465 OpenSIUC database. (Paper 465)

Brian, A. J., Roncadin, C., Duku, E., Bryson, S. E., Smith, I. M., Roberts, W., . . . Zwaigenbaum, L. (2014). Emerging cognitive profiles in high-risk infants with and without autism spectrum disorder. Research in Autism Spectrum Disorders, 8, 1557–1566.

Brignell, A., Williams, K., Prior, M., Donath, S., Reilly, S., Bavin, E.L., Eadie, P., Morgan, A.T. (2017). Parent-reported patterns of loss and gain in communication in 1- to 2-year-old children are not unique to autism spectrum disorder. Autism, 21:3, 344–356. doi: https://doi.org/10.1177/13623613166447

Brock, Jon (2013): Does a baby's eye gaze really predict future autism?. figshare. http://dx.doi.org/10.6084/m9.figshare.878085

Bryson, S., Garon, N., McMullen, T., Brian, J., Zwaigenbaum, L., Armstrong, V., Roberts, W., Smith, I., Szatmari, P. (2017). Impaired disengagement of attention and its relationship to emotional distress in infants at high-risk for autism spectrum disorder. Journal of Clinical and Experimental Neuropsychology. doi: 10.1080/13803395.2017.1372368

Bryson, S. E., Zwaigenbaum, L., Brian, J., Roberts, W., Szatmari, P., Rombough, V., & McDermott, C. (2007). A prospective case series of high-risk infants who developed autism. Journal of Autism & Developmental Disorders, 37:1, 12-24. doi: 10.1007/s10803-006-0328-2

Caravella, K.E., Roberts, J.E. (2017). Adaptive skill trajectories in infants with fragile X syndrome contrasted to typical controls and infants at high risk for autism. Research in Autism Spectrum Disorders, 40, 1-12. doi: 10.1016/j.rasd.2017.05.002

Chenausky, K., Nelson, C., Tager-Flusberg, H. (2017). Vocalization Rate and Consonant Production in Toddlers at High and Low Risk for Autism. Journal of Speech, Language, and Hearing Research 60, 865–876. doi: 10.1044/2016_JSLHR-S-15-0400

Chez, M.G., Guido-Estrada, N. (2010). Immune Therapy in Autism: Historical Experience and Future Directions with Immunomodulatory Therapy. Neurotherapeutics, 7, 293-301

Christensen, D.L., Baio, J., Van Naarden Braun, K., Bilder, D., Charles, J., Constantino, J.N., Daniels, J., Durkin, M.S., Fitzgerald, R.T., Kurzius-Spencer, M., Lee, L.C., Pettygrove, S., Robinson, C., Schulz, E., Wells, C., Wingate, M.S., Zahorodny, W., Yeargin-Allsopp, M., Centers for Disease Control and Prevention (CDC) (2016). Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years--Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. MMWR Surveill Summ., 65:3, 1-23. DOI: 10.15585/mmwr.ss6503a1.

Connolly, A.M., Chez, M.G., Pestronk, A., Arnold, S.T., Mehta, S., Deuel, R.K. (1999). Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders. The Journal of Pediatrics, 134:5, 607-613

Constantino, J.N., Charman, T. (2016). Diagnosis of autism spectrum disorder: reconciling the syndrome, its diverse origins, and variation in expression. Lancet Neurology, 15, 279–91, doi: http://dx.doi.org/10.1016/S1474-4422(15)00151-9

Constantino, J.N., Zhang, Y., Frazier, T., Abbacchi, A.M., Law, P. (2010). Sibling Recurrence and the Genetic Epidemiology of Autism. American Journal of Psychiatry, 167:11, 1349–1356

Daniels, A.M., Mandell, D.S. (2014). Explaining differences in age at autism spectrum disorder diagnosis: A critical review. Autism, 18:5, 583–597

Dawson, G., Osterling, J., Meltzoff, A. N., & Kuhl, P. (2000). Case Study of the Development of an Infant with Autism from Birth to Two Years of Age. J Appl Dev Psychol, 21:3, 299-313. doi: 10.1016/S0193-3973(99)00042-8

De Rubeis, S., Siper, P.M., Durkin, A., Weissman, J., Muratet, F., Halpern, D., Trelles, M.d.P., Frank, Y., Lozano, R., Wang, A.T., Holder Jr, J.L., Betancur, C., Buxbaum, J.D., Kolevzon, A. (2018). Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by SHANK3 point mutations. Molecular Autism, 9:31, 1-20. https://doi.org/10.1186/s13229-018-0205-9

Dhossche, D.M. (2014). Decalogue of catatonia in autism spectrum disorders. Frontiers in Psychiatry, 5:157, 1-4. doi: 10.3389/fpsyt.2014.00157

Elsabbagh, M., Fernandes, J., Webb, S.J., Dawson, G., Charman, T., Johnson, M.H., The Bristish Autism Study of Infant Siblings Team (2013). Disengagement of visual attention in infancy is associated with emerging autism in toddlerhood. Biological Psychiatry, 74:3, 189-194. doi: 10.1016/j.biopsych.2012.11.030

Elsabbagh, M., & Johnson, M. H. (2007). Infancy and autism: progress, prospects, and challenges. Progress in Brain Research, 164, 355-383. doi: 10.1016/S0079-6123(07)64020-5

Elsabbagh, M., & Johnson, M. H. (2010). Getting answers from babies about autism. Trends in Cognitive Sciences, 14:2, 81-87. doi: 10.1016/j.tics.2009.12.005

Estes, A., Zwaigenbaum, L., Gu, H., St. John, T., Paterson, S., Elison, J.T., Hazlett, H., Botteron, K., Dager, S.R., Schultz, R.T., Kostopoulos, P., Evans, A., Dawson, G., Eliason, J., Alvarez, S., Piven, J., IBIS network (2015). Behavioral, cognitive, and adaptive development in infants with autism spectrum disorder in the first 2 years of life. Journal of Neurodevelopmental Disorders, 7:24, 1-10. doi: 10.1186/s11689-015-9117-6

Filliter, J.H., Longard, J., Lawrence, M.A., Zwaigenbaum, L., Brian, J., Garon, N., Smith, I.M., Roncadin, C., Roberts, W., Bryson, S.E. (2015). Positive Affect in Infant Siblings of Children Diagnosed with Autism Spectrum Disorder. Journal Abnormal Child Psychology, 43, 567–575. doi: 10.1007/s10802-014-9921-6

Fombonne, E. (2002). Prevalence of childhood disintegrative disorder. Autism, 6:2, 149-157

Fombonne, E., Chakrabarti, S. (2001). No Evidence for A New Variant of Measles-Mumps-Rubella–Induced Autism. Pediatrics, 108, e58, DOI: 10.1542/peds.108.4.e58

Gadow, K.D., Perlman, G., Weber, R.J. (2017). Parent-Reported Developmental Regression in Autism: Epilepsy, IQ, Schizophrenia Spectrum Symptoms, and Special Education. Journal of Autism & Developmental Disorders, 47, 918–926. doi: 10.1007/s10803-016-3004-1

Gangi, D.N., Schwichtenberg, AJ, Iosif, A-M., Young, G.S., Baguio, F., Ozonoff, S. (2017). Gaze to faces across interactive contexts in infants at heightened risk for autism. Autism, 1 –6. doi: 10.1177/1362361317704421

Gliga, T., Smith, T.J., Likely, N., Charman, T., Johnson, M.H. (2015). Early Visual Foraging in Relationship to Familial Risk for Autism and Hyperactivity/Inattention. Journal of Attention Disorders, 1–9 [epub ahead of print]. doi: 10.1177/1087054715616490

Gliga, T., Jones, E. J., Bedford, R., Charman, T., & Johnson, M. H. (2014). From early markers to neuro-developmental mechanisms of autism. Developmental Review, 34:3, 189-207. doi: 10.1016/j.dr.2014.05.003

Goin-Kochel, R. P., Esler, A. N., Kanne, S. M., & Hus, V. (2014). Developmental regression among children with autism spectrum disorder: Onset, duration, and effects on functional outcomes. Research in Autism Spectrum Disorders, 8, 890–898

Goin-Kochel, R.P., Mire, S.S., Dempsey, A.G. (2015). Emergence of Autism Spectrum Disorder in Children from Simplex Families: Relations to Parental Perceptions of Etiology. Journal Autism & Developmental Disorders, 45, 1451–1463. doi: 10.1007/s10803-014-2310-8

Goldberg, W. A., Osann, K., Filipek, P. A., Laulhere, T., Jarvis, K., Modahl, C., . . . Spence, M. A. (2003). Language and other regression: assessment and timing. Journal of Autism & Developmental Disorders, 33:6, 607-616.

Green, J., Pickles, A., Pasco, G., Bedford, R., Wan, M.W., Elsabbagh, M., Slonims, V., Gliga, T., Jones, E.J.H., Cheung, C.H.M., Charman, T., Johnson, M.H., The British Autism Study of Infant Siblings (BASIS) Team (2017). Randomised trial of a parent-mediated intervention for infants at high risk for autism: longitudinal outcomes to age 3 years. Journal of Child Psychology and Psychiatry, 58:12, 1330-1340. doi: 10.1111/jcpp.12728

Gupta, A.R., Westphal, A., Yang, D.Y., Sullivan, C.A., Eilbott, J., Zaidi, S., Voos, A., Vander Wyk, B.C., Ventola, P., Waqar, Z., Fernandez, T.V., Ercan-Sencicek, A.G., Walker, M.F., Choi, M., Schneider, A., Hedderly, T., Baird, G., Friedman, H., Cordeaux, C., Ristow, A., Shic, F., Volkmar, F.R., Pelphrey, K.A. (2017). Neurogenetic analysis of childhood disintegrative disorder. Mol Autism, 8:19. doi: 10.1186/s13229-017-0133-0

Hansen, R.L., Ozonoff, S., Krakowiak, P., Angkustsiri, K., Jones, C., Deprey, L.J., Le, D-N., Croen, L.A., Hertz-Picciotto, I. (2008). Regression in Autism: Prevalence and Associated Factors in the CHARGE Study. Ambulatory Pediatrics, 8, 25–31. doi: 10.1016/j.ambp.2007.08.006

Hendry, A., Jones, E.J.H., Bedford, R., Gliga, T., Charman, T., Johnson, M.H., the BASIS Team (2018). Developmental change in look durations predicts later effortful control in toddlers at familial risk for ASD. Journal of Neurodevelopmental Disorders, 10:3. doi: 10.1186/s11689-017-9219-4

Hrdlicka, M., Komarek, V., Propper, L., Kulisek, R., Zumrova, A., Faladova, L., . . . Urbanek, T. (2004). Not EEG abnormalities but epilepsy is associated with autistic regression and mental functioning in childhood autism. European Child & Adolescent Psychiatry, 13:4, 209-213. doi: 10.1007/s00787-004-0353-7

Humphrey, A., MacLean, C., Ploubidis, G. B., Granader, Y., Clifford, M., Haslop, M., . . . Tuberous Sclerosis Study, G. (2014). Intellectual development before and after the onset of infantile spasms: a controlled prospective longitudinal study in tuberous sclerosis. Epilepsia, 55:1, 108-116. doi: 10.1111/epi.12484

Humphrey, A., Neville, B.G., Clarke, A., Bolton, P.F. (2006). Autistic regression associated with seizure onset in an infant with tuberous sclerosis. Developmental Medicine & Child Neurology,48:7, 609-11.

Hus, V., Taylor, A., Lord, C. (2011). Telescoping of caregiver report on the Autism Diagnostic Interview – Revised. Journal of Child Psychology & Psychiatry, 52:7, 753–760. DOI:10.1111/j.1469-7610.2011.02398.x.

Ibañez, L.V., Grantz, C.J., Messinger, D.S. (2013). The Development of Referential Communication and Autism Symptomatology in High-Risk Infants. Infancy, 18:5. doi:10.1111/j.1532-7078.2012.00142.x

Iverson, J.M., Northrup, J.B., Leezenbaum, N.B., Parladé, M.V., Koterba, E.A., West, K.L. (2018). Early Gesture and Vocabulary Development in Infant Siblings of Children with Autism Spectrum Disorder. Journal of Autism & Developmental Disorders, 48, 55–71. doi: 10.1007/s10803-017-3297-8

Jack, A., Pelphrey, K.A. (2017). Annual Research Review: Understudied populations within the autism spectrum – current trends and future directions in neuroimaging research. Journal of Child Psychology and Psychiatry, 58:4, 411–435. doi:10.1111/jcpp.12687

Johnson, M.H. (2005). Subcortical Face Processing. Nature Reviews Neuroscience, 6, 766-774.Jones, E. J., Gliga, T., Bedford, R., Charman, T., & Johnson, M. H. (2014). Developmental pathways to autism: a review of prospective studies of infants at risk. Neuroscience & Biobehavioral Reviews, 39, 1-33. doi: 10.1016/j.neubiorev.2013.12.001

Jones, R.M., Risi, S., Wexler, D., Anderson, D., Corsello, C., Pickles, A., Lord, C. (2015). How interview questions are placed in time influences caregiver description of social communication symptoms on the ADI-R. Journal of Child Psychology & Psychiatry, 56:5, 577–585. doi:10.1111/jcpp.12325.

Jones, W., & Klin, A. (2013). Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. Nature, 504:7480, 427-431. doi: 10.1038/nature12715

Kalb, L. G., Law, J. K., Landa, R., & Law, P. A. (2010). Onset patterns prior to 36 months in autism spectrum disorders. Journal of Autism & Developmental Disorders, 40:11, 1389-1402. doi: 10.1007/s10803-010-0998-7

Kiani, R., Lawden, M., Eames, P., Critchley, P., Bhaumik, S., Odedra, S., Gumber, R. (2015). Anti-NMDA-receptor encephalitis presenting with catatonia and neuroleptic malignant syndrome in patients with intellectual disability and autism. BJPsych Bulletin, 39, 32-35, doi: 10.1192/pb.bp.112.041954

Klin, A., Chawarska, K., Paul, R., Rubin, E., Morgan, T., Wiesner, L., & Volkmar, F. (2004). Autism in a 15-month-old child. American Journal of Psychiatry, 161:11, 1981-1988. doi: 10.1176/appi.ajp.161.11.1981

Klin, A., Shultz, S., Jones, W. (2015). Social visual engagement in infants and toddlers with autism: Early developmental transitions and a model of pathogenesis. Neuroscience & Biobehavioral Reviews, 50, 189-203. doi:10.1016/j.neubiorev.2014.10.006

Kuczmarski, R.J., Ogden, C.L., Guo, S.S., Grummer-Strawn, L.M., Flegal, K.M., Mei, Z., Wei, R., Curtin, L.R., Roche, A.F., Johnson, C.L. (2002). 2000 CDC growth charts for the United States: Methods and development. National Center for Health Statistics. Vital Health Stat 11:246, 1-190.

Landa, R., & Garrett-Mayer, E. (2006). Development in infants with autism spectrum disorders: a prospective study. Journal of Child Psychology & Psychiatry, 47:6, 629-638. doi: 10.1111/j.1469-7610.2006.01531.x

Landa, R. J., Gross, A. L., Stuart, E. A., & Bauman, M. (2012). Latent class analysis of early developmental trajectory in baby siblings of children with autism. Journal of Child Psychology & Psychiatry, 53:9, 986-996. doi: 10.1111/j.1469-7610.2012.02558.x

Landa, R. J., Gross, A. L., Stuart, E. A., & Faherty, A. (2013). Developmental trajectories in children with and without autism spectrum disorders: the first 3 years. Child Development, 84:2, 429-442. doi: 10.1111/j.1467-8624.2012.01870.x

Landa, R.J., Holman, K.C., Garrett-Mayer, E. (2007). Social and Communication Development in Toddlers With Early and Later Diagnosis of Autism Spectrum Disorders. Archives of General Psychiatry, 64:7, 853-864

Levin, A.R., Varcin, K.J., O'Leary, H.M., Tager-Flusberg, H., Nelson, C.A. (2017). EEG power at 3 months in infants at high familial risk for autism. Journal of Neurodevelopmental Disorders, 9:34. doi 10.1186/s11689-017-9214-9

Lingam, R., Simmons, A., Andrews, N., Miller, E., Stowe, J., & Taylor, B. (2003). Prevalence of autism and parentally reported triggers in a north east London population. Archives of Diseases in Childhood, 88, 666-670

Lord, C., Luyster, R., Guthrie, W., & Pickles, A. (2012). Patterns of developmental trajectories in toddlers with autism spectrum disorder. Journal of Consulting & Clinincal Psychology, 80:3, 477-489. doi: 10.1037/a0027214

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism & Developmental Disorders, 24:5, 659-685.

Lord, C., Shulman, C., & DiLavore, P. (2004). Regression and word loss in autistic spectrum disorders. Journal of Child Psychology & Psychiatry, 45:5, 936-955. doi: 10.1111/j.1469-7610.2004.t01-1-00287.x

Marquand, A.F., Wolfers, T., Mennes, M., Buitelaar, J., Beckmann, C.F. (2016). Beyond Lumping and Splitting: A Review of Computational Approaches for Stratifying Psychiatric Disorders. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 1:5, 433–447. doi.org/10.1016/j.bpsc.2016.04.002Matson, J.L., Mahan, S. (2009). Current status of research on childhood disintegrative disorder. Research in Autism Spectrum Disorders, 3, 861–867. doi:10.1016/j.rasd.2009.01.006

Messinger, D.S., Young, G.S., Webb, S.J., Ozonoff, S., Bryson, S.E., Carter, A., Carver, L., Charman, T., Chawarska, K., Curtin, S., Dobkins, K., Hertz-Picciotto, I., Hutman, T., Iverson, J.M., Landa, R., Nelson, C.A., Stone, W.L., Tager-Flusberg, H., Zwaigenbaum, L. (2015). Early sex differences are not autism-specific: A Baby Siblings Research Consortium (BSRC) study. Molecular Autism, 6:32, 1-11. doi: 10.1186/s13229-015-0027-y

Miller, M., Iosif, A-M., Hill, M., Young, G.S., Schwichtenberg, A.J., Ozonoff, S. (2017). Response to Name in Infants Developing Autism Spectrum Disorder: A Prospective Study. Journal of Pediatrics, 183, 141-146.

Miller, M., Iosif, A-M., Young, G.S., Hill, M., Hanzel, E.P., Hutman, T., Johnson, S., Ozonoff, S. (2016). School-Age Outcomes of Infants at Risk for Autism Spectrum Disorder. Autism Research, 9, 632–642.

Nordahl, C.W., Lange, N., Li, D.D., Barnett, L.A., Lee, A., Buonocore, M.H., Simon, T.J., Rogers, S., Ozonoff, S., Amaral, D.G. (2011). Brain enlargement is associated with regression in preschool-age boys with autism spectrum disorders. Proceedings of the National Academy of Sciences, 108:50, 20195–20200

Oerlemans, A.M., Hartman, C.A., Franke, B., Buitelaar, J.K., Rommelse, Nanda N.J. (2016). Does the cognitive architecture of simplex and multiplex ASD families differ? Journal of Autism & Developmental Disorders, 46, 489–501

Oslejskova, H., Dusek, L., Makovska, Z., Pejcochova, J., Autrata, R., & Slapak, I. (2008). Complicated relationship between autism with regression and epilepsy. Neuro Endocrinology Letters, 29:4, 558-570.

Ozonoff, S., Gangi, D., Hanzel, E.P., Hill, A., Hill, M.M., Miller, M., Schwichtenberg, A.J., Steinfeld, M.B., Parikh, C., Iosif, A-M. (2018). Onset Patterns in Autism: Variation across Informants, Methods, and Timing. Autism Research, 11, 788–797. doi: 10.1002/aur.1943

Ozonoff, S., Heung, K., Byrd, R., Hansen, R., & Hertz-Picciotto, I. (2008). The onset of autism: patterns of symptom emergence in the first years of life. Autism Research, 1:6, 320-328. doi: 10.1002/aur.53

Ozonoff, S., Iosif, A. M., Baguio, F., Cook, I. C., Hill, M. M., Hutman, T., . . . Young, G. S. (2010). A prospective study of the emergence of early behavioral signs of autism. Journal of the American Academy of Child & Adolescent Psychiatry, 49:3, 256-266.e251-252.

Ozonoff, S., Iosif, A. M., Young, G. S., Hepburn, S., Thompson, M., Colombi, C., . . . Rogers, S. J. (2011a). Onset patterns in autism: correspondence between home video and parent report. Journal of the American Academy of Child & Adolescent Psychiatry, 50:8, 796-806.e791. doi: 10.1016/j.jaac.2011.03.012

Ozonoff, S., Williams, B. J., & Landa, R. (2005). Parental report of the early development of children with regressive autism: the delays-plus-regression phenotype. Autism, 9:5, 461-486. doi: 10.1177/1362361305057880

Ozonoff, S., Young, G.S., Carter, A., Messinger, D., Yirmiya, N., Zwaigenbaum, L., Bryson, S., Carver, L.J., Constantino, J.N., Dobkins, K., Hutman, T., Iverson, J.M., Landa, R., Rogers, S.J., Sigman, M., Stone, W.L. (2011b). Recurrence Risk for Autism Spectrum Disorders: A Baby Siblings Research Consortium Study. Pediatrics, 128:3, e1-8. doi: 10.1542/peds.2010-2825

Parr, J.R., Le Couteur, A., Baird, G., Rutter, M., Pickles, A., Fombonne, E., Bailey, A.J., The International Molecular Genetic Study of Autism Consortium (IMGSAC) (2011). Early Developmental Regression in Autism Spectrum Disorder: Evidence from an International Multiplex Sample. Journal of Autism & Developmental Disorders, 41, 332–340, doi: 10.1007/s10803-010-1055-2

Peters, S.U., Hundley, R.J., Wilson, A.K., Carvalho, C.M.B., Lupski, J.R., Ramocki, M.B. (2013). Brief Report: Regression Timing and Associated Features in MECP2 Duplication Syndrome. Journal of Autism & Developmental Disorders, 43:10, 2484-90. doi: 10.1007/s10803-013-1796-9

Pickles, A., Simonoff, E., Conti-Ramsden, G., Falcaro, M., Simkin, Z., Charman, T., . . . Baird, G. (2009). Loss of language in early development of autism and specific language impairment Journal of Child Psychology and Psychiatry, 50:7, 843–852.

Robinson, R. O., Baird, G., Robinson, G., & Simonoff, E. (2001). Landau-Kleffner syndrome: course and correlates with outcome. Developmental Medicine & Child Neurology, 43:4, 243-247.

Rogers, S. J. (2004). Developmental regression in autism spectrum disorders. Mental Retardation & Developmental Disabilities Research Reviews, 10:2, 139-143. doi: 10.1002/mrdd.20027

Rogers, S. J. (2009). What are infant siblings teaching us about autism in infancy? Autism Research, 2:3, 125-137. doi: 10.1002/aur.81

Rosario, M., Gillespie-Lynch, K., Johnson, S., Sigman, M., Hutman, T. (2014). Parent-reported Temperament Trajectories among Infant Siblings of Children with Autism. Journal Autism Developmental Disorders, 44:2, 381–393. doi:10.1007/s10803-013-1876-x

Sacrey, L.R., Bryson, S.E., Zwaigenbaum, L. (2013). Prospective examination of visual attention during play in infants at high-risk for autism spectrum disorder: A longitudinal study from 6 to 36 months of age. Behavioural Brain Research, 256, 441–450. doi: 10.1016/j.bbr.2013.08.028

Sacrey, L.R., Zwaigenbaum, L., Szatmari, P., Bryson, S., Georgiades, S., Brian, J., Smith, I.M., Vaillancourt, T., Garon, N., Roncadin, C., Elsabbagh, M. (2017). Brief Report: Characteristics of preschool children with ASD vary by ascertainment. Journal of Autism & Developmental Disorders, 47, 1542–1550

Schwichtenberg, A.J., Young, G.S., Sigman, M., Hutman, .T, Ozonoff, S. (2010). Can family affectedness inform infant sibling outcomes of autism spectrum disorders? Journal of Child Psychology and Psychiatry, 51:9, 1021–1030. doi:10.1111/j.1469-7610.2010.02267x.

Scott, O., Shi, D., Andriashek, D., Clark, B., Goez, H.R. (2017). Clinical clues for autoimmunity and neuroinflammation in patients with autistic regression. Developmental Medicine & Child Neurology. doi: 10.1111/dmcn.13432

Sebat, J., Lakshmi, B., Malhotra, D., Troge, J., Lese-Martin, C., Walsh, T., Yamrom, B., Yoon, S., Krasnitz, A., Kendall, J., Leotta, A., Pai, D., Zhang, R., Lee, Y-H., Hicks, J., Spence, S.J., Lee, A.T., Puura, K., Lehtimäki, T., Ledbetter, D., Gregersen, P.K., Bregman, J., Sutcliffe, J.S., Jobanputra, V., Chung, W., Warburton, D., King, M-C., Skuse, D., Geschwind, D.H., Gilliam, T.C., Ye, K., Wigler, M. (2007). Strong Association of De Novo Copy Number Mutations with Autism. Science, 316:5823, 445–449. doi:10.1126/science.1138659

Shattuck, P. T., Durkin, M., Maenner, M., Newschaffer, C., Mandell, D. S., Wiggins, L., . . . Cuniff, C. (2009). Timing of identification among children with an autism spectrum disorder: findings from a population-based surveillance study. Journal of the American Academy of Child & Adolescent Psychiatry, 48:5, 474-483. doi: 10.1097/CHI.0b013e31819b3848

Shephard, E., Milosavljevic, B., Pasco, G., Jones, E.J.H., Gliga, T., Happé, F., Johnson, M.H., Charman, T. and The BASIS Team (2017). Mid-Childhood Outcomes of Infant Siblings at Familial High-Risk of Autism Spectrum Disorder. Autism Research, 10, 546–557. doi: 10.1002/aur.1733

Shoffner, J., Hyams, L., Langley, G.N., Cossette, S., Mylacraine, L., Dale, J., Ollis, L., Kuoch, S., Bennett, K., Aliberti, A., Hyland, K. (2010). Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression. Journal of Child Neurology, 25:4, 429-434. doi:10.1177/0883073809342128

Shumway, S., Thurm, A., Swedo, S.E., Deprey, L., Barnett, L.A., Amaral, D.G., Rogers, S.J., Ozonoff, S. (2011). Brief Report: Symptom Onset Patterns and Functional Outcomes in Young Children with Autism Spectrum Disorders. Journal of Autism & Developmental Disorders, 41:12, 1727–1732. doi:10.1007/s10803-011-1203-3.

Srivastava, C., Bolton, P.F. (2013). Regression in Development after Seizure Onset in Tuberous Sclerosis: A Report of Two Cases. American Journal of Autism, 1, 1-16. DOI:10.7726/aja.2013.1001

St. John, T., Estes, A.M., Dager, S.R., Kostopoulos, P., Wolff, J.J., Pandey, J., Elison, J.T., Paterson, S.J., Schultz, R.T., Botteron, K., Hazlett, H., Piven, J. (2016). Emerging Executive Functioning and Motor Development in Infants at High and Low Risk for Autism Spectrum Disorder. Frontiers in Psychology. 7:1016. doi: 10.3389/fpsyg.2016.01016

Szatmari, P. (2017). Risk and resilience in autism spectrum disorder: a missed translational opportunity? Developmental Medicine & Child Neurology. doi: 10.1111/dmcn.13588

Szatmari, P., Chawarska, K., Dawson, G, Georgiades, S., Landa, R., Lord, C., Messinger, D.S., Thurm, A, Halladay, A. (2016). Prospective Longitudinal Studies of Infant Siblings of Children With Autism: Lessons Learned and Future Directions. Journal of the American Academy of Child & Adolescent Psychiatry, 55:3, 179-87. doi: 10.1016/j.jaac.2015.12.014.

Thomas, M.S.C., Annaz, D., Ansari, D., Scerif, G., Jarrold, C., Karmiloff-Smith, A. (2009). Using Developmental Trajectories to Understand Developmental Disorders. Journal of Speech, Language, and Hearing Research, 52, 336–358.

Thomas, M.S.C., Davis, R., Karmiloff-Smith, A., Knowland, V.C.P., Charman, T. (2016). The over-pruning hypothesis of autism. Developmental Science, 19:2, 284–305. doi: 10.1111/desc.12303

Thurm, A., Manwaring, S. S., Luckenbaugh, D. A., Lord, C., & Swedo, S. E. (2014). Patterns of skill attainment and loss in young children with autism. Developmental Psychopathology, 26:1, 203-214. doi: 10.1017/S0954579413000874

Thurm, A., Powell, E.M., Neul, J.L., Wagner, A., Zwaigenbaum, L. (2018). Loss of Skills and Onset Patterns in Neurodevelopmental Disorders: Understanding the Neurobiological Mechanisms Autism Research, 11, 212-222. doi: 10.1002/aur.1903

Venker, C. E., Ray-Subramanian, C. E., Bolt, D. M., & Ellis Weismer, S. (2014). Trajectories of autism severity in early childhood. Journal of Autism & Developmental Disorders, 44:3, 546-563. doi: 10.1007/s10803-013-1903-y

Volkmar, F.R., Rutter, M. (1995). Childhood Disintegrative Disorder: Results of the DSM-IV Autism Field Trial. Journal of the American Academy of Child & Adolescent Psychiatry, 34:8, 1092-1095

Wasilewska, J., Kaczmarski, M., Stasiak-Barmuta, A., Tobolczyk, J., Kowalewska, E. (2012). Low serum IgA and increased expression of CD23 on B lymphocytes in peripheral blood in children with regressive autism aged 3-6 years old. Archives Medical Science, 8:2, 324-331. doi: 10.5114/aoms.2012.28561

Webb, S. J., Nalty, T., Munson, J., Brock, R., Abbott, R., & Dawson, G. (2007). Rate of head circumference growth as a function of autism diagnosis and history of autistic regression. Journal of Child Neurology, 22, 1182-1190

Werner, E., & Dawson, G. (2005). Validation of the phenomenon of autistic regression using home videotapes. Archives of Genernal Psychiatry, 62:8, 889-895. doi: 10.1001/archpsyc.62.8.889

WHO (1993). The ICD-10 classification of mental and behavioural disorders: diagnostic criteria. Geneva: World Health Organization.

WHO (2018). The WHO Child Growth Standards. Retrieved August 8, 2018, from www.who.int/childgrowth/en/ Williams, K., Brignell, A., Prior, M., Bartak, L., & Roberts, J. (2015). Regression in autism spectrum disorders. Journal of Paediatrics & Child Health, 51:1, 61-64. doi: 10.1111/jpc.12805

Yirmiya, N., & Charman, T. (2010). The prodrome of autism: early behavioral and biological signs, regression, peri- and post-natal development and genetics. Journal of Child Psychology & Psychiatry, 51:4, 432-458. doi: 10.1111/j.1469-7610.2010.02214.x

Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., & Szatmari, P. (2005). Behavioral manifestations of autism in the first year of life. International Journal of Developmental Neuroscience, 23:(2-3, 143-152.

Zwaigenbaum, L., Thurm, A., Stone, W., Baranek, G., Bryson, S., Iverson, J., . . . Sigman, M. (2007). Studying the emergence of autism spectrum disorders in high-risk infants: methodological and practical issues. Journal of Autism & Developmental Disorders, 37:3, 466-480. doi: 10.1007/s10803-006-0179-x

Table 1. Prospective studies showing evidence of regression. Longitudinal studies using repeated measures and reporting data at the individual level and/or raw scores are included.

Study (same superscript denotes reports of same sample)	**N**	**Sample selection**	**Schedule of assessments**	**Repeated measures (data type)**	**Raw or age-standardised scores**	**Group or individual data**	**Evidence of regression**
Case reports							
Dawson, Osterling, Meltzoff and Kuhl (2000)	1	Younger sibling of child with Asperger syndrome; clinical referral for feeding problems	• 2.5 months • 4 months • 9 months • 11-13 months • 13-15 months • 24 months	• Qualitative reports • BSID-II at 11-13 months (age-standardised) • MSEL at 24 months (age-standardised)	Qualitative and standardised	Individual	**Yes**; from clinical observation, loss of social communicative behaviours. Reduced use of eye-contact, imitative games and imitative vocal responses. **Partial**; from standardised test scores: decline from 12th to 1st percentile (unclear if loss or plateau).
Klin et al. (2004)	1	Younger sibling of child with autism; clinical referral because stopped vocalising	• 15 months • 23 months • 34 months	• MSEL (age equivalent) • CDI (age equivalent) • VABS (age equivalent) • ADOS (algorithm score, qualitative reports)	Age equivalent scores	Individual	**Partial**; from parent report. Loss of words and social engagement. **No** evidence of loss from age equivalent scores; minimal gain resulted in decline in standardised scores.
Bryson et al. (2007)	9	High risk infant siblings	• 6 months • 12 months • 16 months • 24 months • 36 months	• BSID or MSEL (age standardised scores) • CDI: Words and Gestures (qualitative reports) • AOSI (algorithm score, qualitative reports) • ADOS (algorithm score, qualitative reports)	Qualitative and standardised	Individual	**Yes**; all children showed some loss of social-emotional connectedness over time on clinical assessment/qualitative report. Loss of expressive language in one case. **Partial**; decline in standardised IQ scores in 6 children from near average IQ to severe cognitive impairment

Study (same superscript denotes reports of same sample)	N	Sample selection	Schedule of assessments	Repeated measures (data type)	Raw or age-standardised scores	Group or individual data	Evidence of regression
				• Temperament: ITS or TBAQ (qualitative reports) • Semi-structured interview surveying parental concerns (qualitative reports)			between 12 and 24 or 36 months (unclear if loss or plateau).
Studies focusing on social communication, cognitive development, adaptive behavior, temperament							
Landa and Garrett-Mayer (2006)[A]	60 + 27	High risk infant sibs + low risk controls	• 6 months • 14 months • 24 months • 30 months • 36 months	• MSEL (raw and age standardised scores)	Raw and standardised	Group and individual	**Yes**; 42% of infants with ASD showed decline in MSEL raw scores from 14 to 24 months, 33% showed clinical worsening in social and communication functioning, 33% lost raw score points in language domains. Further 17% showed clinical regression in social and communication functioning but did not lose MSEL raw scores.
Landa, Holman, and Garrett-Mayer (2007)[A]	107 + 18	High risk infant sibs + low risk controls	• 14 months • 24 months	• CSBS DP (frequency or variety of social and communicative behaviors)	Raw	Group	**Yes**; decrease in shared positive affect in groups with ASD from 14 to 24 months of age; decrease in gesture inventory from 14 to 24 months in later-diagnosis ASD group.

Study (same superscript denotes reports of same sample)	N	Sample selection	Schedule of assessments	Repeated measures (data type)	Raw or age-standardised scores	Group or individual data	Evidence of regression
Landa, Gross, Stuart and Faherty (2013)[A]	204 + 31	High risk infant sibs + low risk controls	• 6 months • 14 months • 18 months • 24 months • 30 months • 36 months	• MSEL (raw and age standardised scores) • CSBS DP: initiation of joint attention; shared positive affect; consonant diversity (frequency or variety of social and communicative behaviors)	Raw and standardised	Group and individual	**Yes**; loss of raw score MSEL points for both expressive and receptive language in 29% of early onset ASD group, 19% of later onset ASD group, and 2% of the non-ASD group.
Ozonoff et al. (2010)	25 + 25	High risk infant sibs + low risk controls	• 6 months • 12 months • 18 months • 24 months • 36 months	• MSEL (raw scores) • Social Communication Behaviour Codes (duration/frequency) • Examiner Ratings of Social Engagement (ordinal rating)	Raw and standardised	Group and individual	Social communication: **Yes;** 86% of infants subsequently diagnosed with ASD showed decrease in frequency of gaze to faces over time. Cognitive and language (MSEL): **No** loss, but plateau at group level; no individual data (though retrospective report of language loss in one child).
Ozonoff et al. (2018)	149 + 81	High risk infant sibs + low risk controls	• 6 months • 9 months • 12 months • 15 months • 18 months • 24 months	• Examiner Ratings of Eye Contact, Social Affect, and Social Engagement (ordinal rating) • Early Development Questionnaire (EDQ)	Raw	Group and individual	Yes: latent class growth models identified 88% of infants with ASD with decline in social engagement over time by examiner prospective ratings, and 69% by parent prospective report; 47% had categorical parent report of

Study (same superscript denotes reports of same sample)	N	Sample selection	Schedule of assessments	Repeated measures (data type)	Raw or age-standardised scores	Group or individual data	Evidence of regression
			• 36 months	(ordinal rating and categorical judgement)			regression using prospective measure and 29% using retrospective measure.
Rosario et al. (2014)	54	High risk infant sibs	• 6 months • 12 months • 18 months • 24 months • 36 months	• Carey Temperament Scales (version appropriate for age)	Raw	Group	Possibly; group of infants with ASD showed decreasing adaptability and approach behavior from 6 to 36 months.
St John et al. (2016)	186 + 76	High risk infant sibs + low risk controls	• 12 months • 24 months	• Executive function, A-not-B task: working memory and inhibition (proportion trials correct)	Raw	Group	Possibly; high risk infant sib groups (ASD and non-ASD) showed slightly poorer inhibition at 24 months than 12 months.
Brignell et al. (2017)	41 + 110 + 831	ASD + language impairment + typically developing (general population sample)	• 8 months • 12 months • 24 months • 4 years • 5 years • 6 years • 7 years	• CDI: Words and Gestures, Words and Sentences (expressive vocabulary raw scores) • CSBS-ITC: Infant Toddler Checklist (raw scores)	Raw	Group and individual trajectories	Yes, 1 child in ASD group and 1 in language impairment (LI) group had lower CDI vocabulary score at 24 months than 12 months. 41% in ASD group, 30% in LI group, and 26% in typically developing group had lower raw score in at least one cluster of skills from CSBS-ITC at 24 months compared to 12 months; ASD group were more likely than other groups to have lower scores in more than one domain.
Miller et al. (2017)	95 + 60	High risk infant sibs + low risk controls	• 6 months • 9 months • 12 months • 15 months • 18 months • 24 months	• AOSI: Orients to name (ordinal rating)	Raw	Group and within individual change	Possibly; 54% of infants with ASD who oriented to name at 12 months failed to respond during at least one subsequent visit. However, 30% of infants without also ASD failed to respond at least once between 12 and 24 months.

Study (same superscript denotes reports of same sample)	N	Sample selection	Schedule of assessments	Repeated measures (data type)	Raw or age-standardised scores	Group or individual data	Evidence of regression
Studies focusing on visual attention							
Zwaigenbaum et al. (2005)[B]	65 + 23	High risk infant sibs + low risk controls	• 6-7 months • 12-14 months • 24 months	• Visual orienting / gap-overlap task (latency to disengage) • AOSI (algorithm scores) • IBQ	Raw and algorithm scores	Group and within individual change	Yes; a subset of high-risk siblings (25%) showed decline in ability to disengage and shift attention from one of two competing visual stimuli between 6 and 12 months of age. Visit-to-visit change not reported for other measures.
Bryson et al. (2017)[B]	83 + 53	High risk infant sibs + low risk controls	• 6 months • 12 months • 36 months	• Visual orienting / gap-overlap task (latency to disengage) • MSEL (age standardised scores) • IBQ (ordinal rating)	Raw and standardised	Group	Yes; high-risk sibling ASD group showed decline in ability to disengage and shift attention from one of two competing visual stimuli between 6 and 12 months of age. Visit-to-visit change not reported for other measures.
Elsabbagh et al. (2013)	54 + 50	High risk infant sibs + low risk controls	• 6-10 months • 12-15 months • 24 months • 36 months	• Gap-overlap task (latency to disengage) • MSEL (age standardized scores) • VABS (age standardized scores)	Raw and standardized	Group and individual	Yes; infants with ASD (n=16) showed no developmental gain in ability to disengage from central stimulus at 14 months when compared to 7 months. 40% with ASD had longer latency (indicating poorer performance) at 14 months compared to 7 months.
Jones and Klin (2013)	59 + 51	High risk infant sibs + low risk controls	• 2 months • 3 months • 4 months • 5 months • 6 months • 9 months • 12 months • 15 months	• Eye-tracking paradigm: gaze to eyes while viewing scenes of naturalistic caregiver interaction (percentage of visual fixation time to regions of interest)	Raw	Group and individual	Yes; infants with ASD (males only, n=11) showed decline in eye fixation from 2 until 24 months of age, with average levels of eye fixation beginning in the range of TD infants (males only, n=25). Declining trajectory predicted ASD.

Study (same superscript denotes reports of same sample)	N	Sample selection	Schedule of assessments	Repeated measures (data type)	Raw or age-standardised scores	Group or individual data	Evidence of regression
			• 18 months • 24 months				

Note. ADOS, Autism Diagnostic Observation Schedule; AOSI, Autism Observation Scale for Infants; BSID-II, Bayley's Scales of Infant Development, 2nd edition; CDI, MacArthur Communicative Development Inventory; CSBS DP, Communication and Symbolic Behavior Scale Developmental Profile; CSBS-ITC, Communication and Symbolic Behavior Scale – Infant Toddler Checklist; IBQ, Infant Behavior Questionnaire; ITS, Infant Temperament Scale; MSEL, Mullen Scales of Early Learning; TBAQ, Toddler Behavior Assessment Questionnaire; VABS, Vineland Adaptive Behaviour Scales. A, B: same superscript denotes reports of same sample.

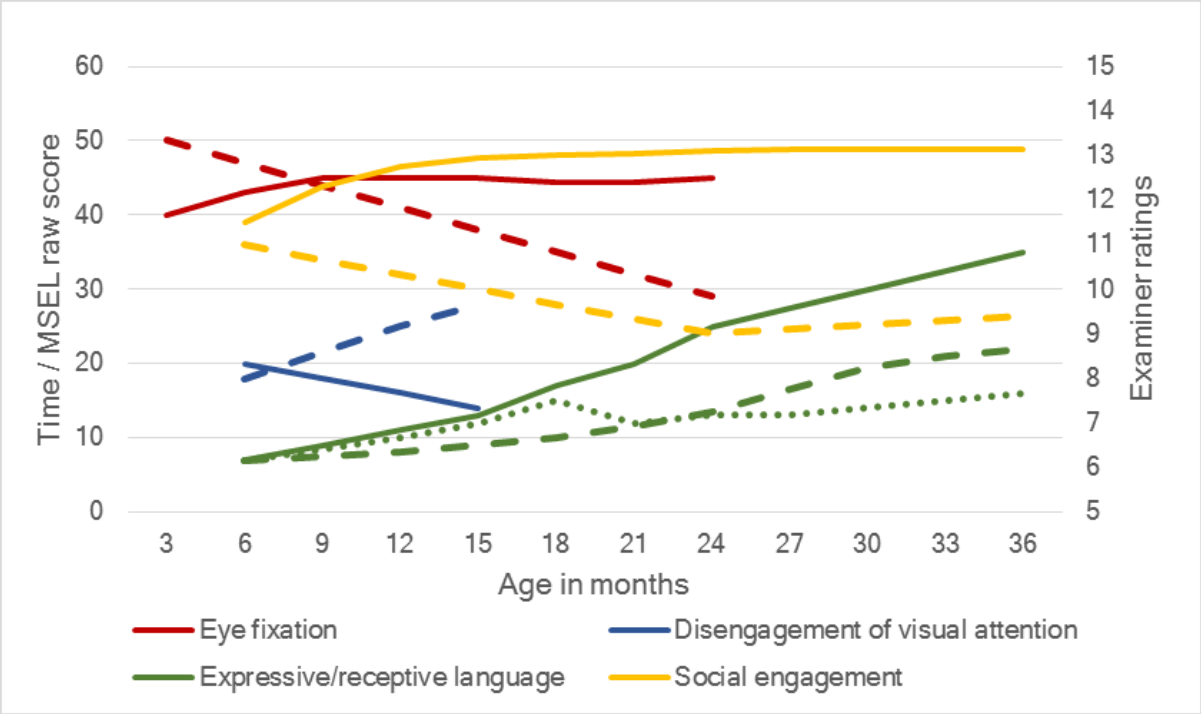

Figure 1. Key findings on disengaging visual attention, eye fixation, social engagement, and language. Results are summarised and approximated from the following literature. (i) Disengagement of visual attention (blue) is based on Figure 1 from Elsabbagh et al. (2013); left hand axis here shows difference in time to disengage attention in overlap vs. baseline condition (20=200ms); *increasing* time to disengage represents loss of skill. (ii) Eye fixation (red) is based on Figure 2 from Jones and Klin (2013); left hand axis here shows percentage fixation time; (iii) Expressive/receptive language (green) is based on Figure 1 from Landa et al. (2013), other than the trajectory for the subgroup with loss of raw score points, which was not presented in Landa et al. but has been estimated here; left hand axis here shows MSEL raw scores. (iv) Social engagement (yellow) is based on Figure 1 from Ozonoff et al. (2018); right hand axis here shows examiner ratings. Approximate periods during which subcortical and cortical mechanisms of social orienting and attentional control are likely to be in decline or developing are indicated. *Note*. Solid lines: Infants without ASD; dashed lines: Infants with ASD; dotted line: Subgroup of infants with ASD who lost raw score points for language.

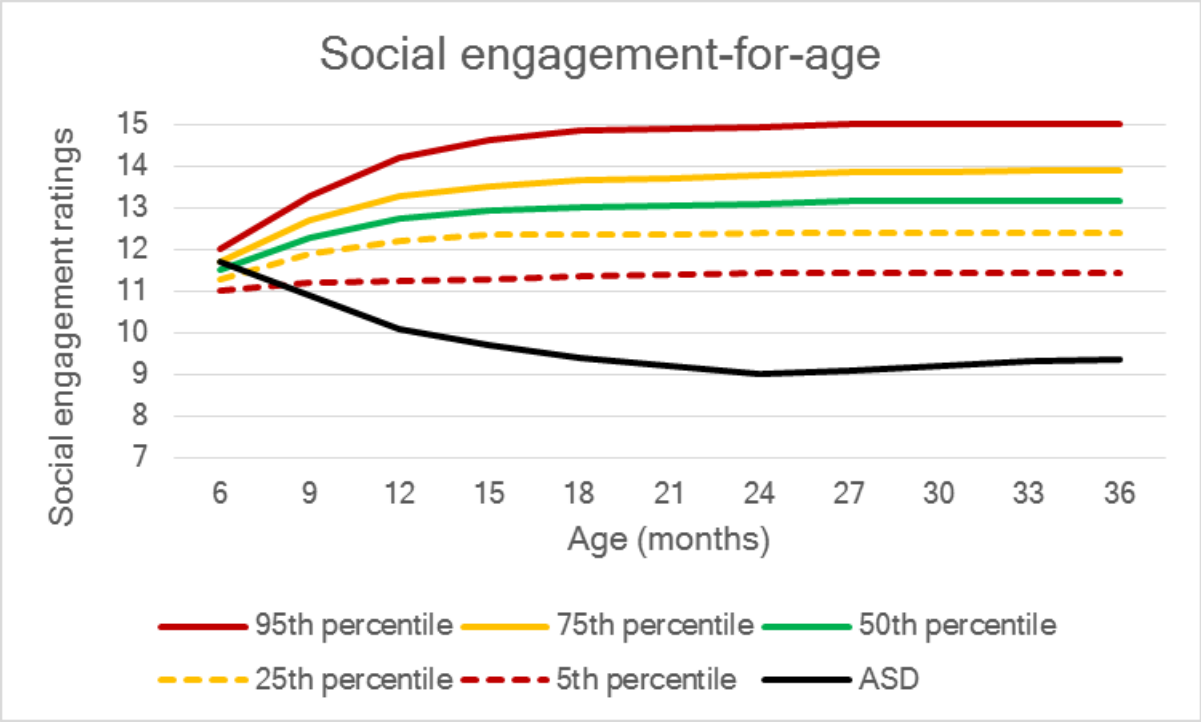

Figure 2. Hypothetical growth curves for ratings (examiner or parent) of frequency of social engagement behaviors (e.g., eye contact, shared affect). Based on Figure 1 from Ozonoff et al. (2018), this figure portrays what growth curves based on smoothed percentile curves could look like. In this example, an infant who subsequently develops ASD may show a decline in ratings of social engagement from the 75th to the 5th percentile between 6 and 9 months of age that would flag potential risk status.