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The prodrome of autism: Early behavioral and biological signs, regression, peri- and post-natal development and genetics.

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## **Abstract**

Autism is one of the most heritable neurodevelopmental conditions and has an early onset, with symptoms being required to be present in the first 3 years of life in order to meet criteria for the ‘core’ disorder in the classification systems. As such, the focus on identifying a prodrome over the past 20 years has been on pre-clinical signs or indicators that will be present very early in life, certainly in infancy. A number of novel lines of investigation have been used to this end, including retrospective coding of home videos, prospective population screening and ‘high risk’ sibling studies; as well as the investigation of pre- and peri-natal, brain developmental and other biological factors. Whilst no single prodromal sign is expected to be present in all cases, a picture is emerging of indicative prodromal signs in infancy and initial studies are being undertaken to attempt to ameliorate the early presentation and even ‘prevent’ emergence of the full syndrome.

## **Introduction**

Along with other neurodevelopmental disorders with childhood onset, interest in studying the prodrome of autism spectrum disorders (ASDs) has grown considerably over the past decade. Many of the reasons for this are shared in common with other conditions covered in this special issue. The primary motivation for identifying the earliest signs of emerging ASDs is the desire to develop and test early or even 'preventative' interventions to lessen morbidity by changing the course of early emerging developmental perturbation, thus preventing 'secondary' neurodevelopmental disturbances (Dawson, 2008; Mundy, Sullivan, & Mastergeorge, 2009).

In medicine, prodrome refers to the early sign/s or symptom/s indicating the development of a disease, or indicating that a disease attack is imminent. It is the premonitory or warning symptom for a certain disease. Thus, "prodrome" status refers to the time frame beginning with the initial onset of clinical signs that do not meet the diagnostic criteria required for the disease or disorder, up to the time in which the clinical symptoms fulfill the required criteria for the disease or disorder. Therefore, the prodrome is always defined retrospectively, and necessitates that the disease will follow the earlier clinical signs, markers or precursors which constitute the prodrome. These prodromal early signs may be biological or/and behavioral and once identified may be informative to attempts to eliminate, prevent and/or treat the disease itself. Yet, a disease or a disorder may also appear with no identifiable preceding prodrome.

In the field of developmental psychopathology, risk factors are referred to as factors that may characterize a certain group of individuals, some of whom will also manifest the associated vulnerability with the vulnerability referring to the prodrome and/or the disease/disorder. Thus, whereas the prodrome refers to signs that precede

the disease, risk factors characterize a certain group of individuals (e.g., siblings of children with ASD who are at genetically higher risk to develop ASD), some of whom will develop the prodrome and/or the disease and some who will not. Vulnerability characterizes the affected individuals within the group at risk (i.e., only those siblings who indeed develop ASD). Although we would like to be able to identify all affected individuals with a certain vulnerability and delineate the emergence of the prodrome of the disease/disorder, typically it is easier to identify the general risk factor/s rather than the specific vulnerability. This results in the identification of a larger group of at-risk individuals of whom later on, at some time in the future, a smaller subgroup will, or will not, reveal the prodrome and/or the disease/disorder. Early markers which define risk might not be precursors or part of the prodrome or the disease; yet the prodrome of any given disorder, in its most narrow interpretation, implies identification of the early symptoms of the disease. Yet in the field of ASDs, as with other disorders and diseases as well, we are more advanced in defining risks factors as possible precursors rather than a specific clinical picture of a prodrome which most often than not leads to the disease.

As Rutter (1993), Werner and Smith (1982), and others have shown risk factors may be genetic or due to biological, family and/or social environmental factors and processes that affect the course of development. Risk factors may operate independently or interactively in that genetic susceptibility may interact with certain environmental factors and thus increase the risk for a certain disease. Furthermore, a prodrome for a certain disease needs to be as specific and universal as possible for it to be of clinical utility (for example; to initiate a preventative intervention). Specificity requires that it is only present in the specific class of diseases/disorders, ASDs in our case. Universality requires that all, or almost all, individuals who

develop the disease also show the prodrome prior to appearance of the full blown clinical picture of an ASD. As ASDs include a group of behavioral syndromes that are most likely common to more than one etiological mechanism (Geschwind, 2008; Geschwind & Levitt, 2007; Levitt & Campbell, 2009); it is probably very difficult, if not impossible, to conceive of a specific and universal prodrome of ASDs. Rather, the risk factors and prodromes may be as diverse as the many etiologies and developmental trajectories underlying ASDs.

Several sources of data are available to researchers and clinicians who are trying to delineate the early risk markers and prodrome/s of ASDs. First, many single and multiple case studies regarding children with autism and other related syndromes are available to the interested reader. Many parents have written books about their experience raising their children with autism; including some with very rich case materials (e.g., Park, 1967). In addition to case reports, the literature on early markers for ASD includes both retrospective and prospective studies regarding the early development of children who later on are diagnosed with ASD. Retrospective information is mostly collected via parental reports using various questionnaires and interviews and/or home videos of the children, taken prior to the child receiving the diagnosis. Although retrospectively collected clinical information and parental accounts are important and provide tantalizing glimpses into what might be the earliest manifestations of autism; these accounts may be subjected to reporting biases of several kinds that leave open the accuracy of the early characteristics that are recalled many years later. In addition to retrospective studies and reports, currently, many prospective studies are carried out. These studies involve samples of young children from the general population who have some initial risk marker such as, for example, being identified as 'at risk' by failing a screening questionnaire and/or being

a younger sibling of a child diagnosed with ASD who is at genetically higher risk compared to other children.

The aim of the current paper is to provide a state of the art summary regarding the early signs, risk factors and prodrome of ASDs. We will examine common early markers for ASDs first, as evidenced in retrospective and prospective studies of samples children with ASDs as well as children who are at risk for ASDs, followed by a review of the pre-, and peri-natal risk factors, and a section on genetics and ASD in the context of risk markers and the prodrome and etiology of ASDs. We will conclude with some ethical issues regarding early diagnosis and prevention/ intervention and some thoughts for future studies.

Our scientific ability to learn about the prodrome of ASDs is strongly associated with the available technology and with the diagnostic criteria in existence. When autism was a considerably rare behavioral disorder with a prevalence rate of 4-5 cases per 10,000 live births (Lotter, 1966; see Fombonne, 2009, for a review) it was impossible and not cost effective to conduct large screening studies. Such studies are now much more feasible given that prevalence rates for the broadly defined autism spectrum are now estimated to be between 1 in 100 to 1 in 150 (Baird et al., 2006; CDC, 2007). Similarly, during the early years of the field we had to rely on parental reports about early development knowing that the validity of these reports may not be high due to factors such as selective memory and seeing things through the prism of the disorder. With video recording becoming a common practice in many families in western society, scientists were able to corroborate parental reports by collecting and analyzing home video recordings of the children filmed prior to receiving an ASD diagnosis. With the widening of the diagnostic criteria and the emergence of new

technologies it was possible to start conducting large scale prospective studies regarding the development of children with ASDs and children at risk for ASDs.

**What can we learn about the prodrome of ASDs from home video studies?**

Evidence for developmental difficulties in infants who are later diagnosed with ASDs is provided by investigators who analyzed home movies made available by parents. These retrospective studies offer an opportunity to explore the early behavioral characteristics of children with ASDs, with the advantage of enabling unbiased, trained observers who are blind to later diagnoses to examine the child's behavior over time and across different situations as well as in a natural context. Although this methodology has some advantages in that natural occurring behavior prior to diagnosis is evaluated, home videos also suffer from some limitations as the data is not standardized and parents may chose to videotape their children when the children are at their best and not necessarily while manifesting some of the behaviors which may be of most interest to researchers studying the early emergence of ASDs. Studies vary in the use of comparison groups (e.g. typically developing children vs. children with an intellectual disability but not an ASD), the types of behavior coded, and the time window in which video captured materials were available (See Table 1; for a summary of studies).

Losche (1990) was the first to analyze home videos of children who were later diagnosed with ASDs in comparison to a group of typically developing children (age ranged from 4 to 42 months). Impairments in sensorimotor development, joint social activities, and symbolic play were evident in the ASD group compared to the typically developing group. Adrien et al. (1993; 1991) examined home movies of infants (birth to 24 months) and found that early symptoms prior to age of 12 months that were

associated with later ASDs included abnormalities in social attention, interaction, communication and emotion (i.e., lack of social smiling, eye contact, and appropriate facial expressions) as well as abnormalities in motor behaviors.

Osterling and Dawson (1994) and Werner, Dawson, Osterling, and Dinno (2000) reported that infants who later developed autism showed significantly less eye contact and less responsiveness to their name being called as well as impairments in affect and in joint attention behaviors (i.e., showing and pointing) compared to typically developing infants, during home video recordings of their first year birthday parties and that furthermore, social deficits such as less orienting to their name or less looking at the face of another while smiling in dyadic interactions, already appeared in the home videos of these children which were taken between 8-10 months of age. Osterling, Dawson, and Munson (2002) extended this work to include a group of infants later diagnosed with intellectual disability, as well as a group of typically developing infants, and found that infants in the ASD group looked at others and oriented to their name less frequently than infants in the intellectual disability group. Werner and Dawson (2005) separated out ASD infants with regression and those without regression (sometimes called 'early onset' autism) and found that those with no regression ('early onset') displayed fewer joint attention and communicative behaviors compared to infants with autistic regression and infants with typical development at 12 months. No significant differences emerged at 12 months between infants with ASDs who experienced regression and infants with typical development in the use of joint attention, and indeed children with ASDs who experienced regression had *more* frequent use of words and babble compared to infants with no regression. This study for the first time used the home video methodology to corroborate the parental report of intact early skills followed by an apparent loss of

skills. At 24 months, compared to infants with typical development, both groups of infants with later ASDs had lower frequencies of using words, vocalizations, declarative pointing, social gaze, and orienting to name.

Mars, Mauk, and Dowrick (1998) found that difficulties in social and communicative behaviors such as joint attention deficits were less frequent in the videos of infants with later diagnoses of PDD-NOS than in the videos of children with autistic disorder between 12 and 30 months. Bernabei, Camaioni, and Levi (1998) examined the social interaction, communication, language and functional and symbolic play of infants later diagnosed with autism from birth to 24 months (0-6, 6-12, 12-18 and 18-24 months). They reported on low frequency of communicative gestures (i.e., pointing, showing, and ritualized requests), pretend play and conventional social games from 6 to 12 months as well as on regression in socio-interactive behaviors. Baranek (1999; Baranek, et al., 2005) found that impairments in response to name calling, aversion to touch, and orientation to visual stimuli differentiated between infants at 9-12 months who later on received an ASD diagnosis and infants who were later on diagnosed with developmental delays, yet play with objects did not differ among the groups (Baranek et al., 2005). [Colgan et al. \(2006\)](#) also examined the emergence of gestures used in social interactions (i.e., frequency, initiation, prompting, and types of gestures) and reported that restricted types of gestures were strongly associated with the ASD group. However neither the frequency of gestures nor the initiation of gestures were significantly associated with being later assigned to the ASD group.

Maestro et al. (2001) examined the development of symbolic activity and intersubjective behaviors (i.e., an early manifestation of the ability to represent other's state of mind) of infants who later developed ASDs compared to infants with typical

development during the first two years of life. Infants who later developed ASDs had more abnormalities in intersubjective behaviors, such as anticipation of another's aim and imitation in the first 6 months of life, and more abnormalities in the course of symbolic activity between 6 and 24 months. In subsequent analysis, Maestro et al. (2002; 2005) reported that infants later diagnosed with ASDs had poor attention to social stimuli, but not to non-social stimuli (objects) in the first 6 months of life. In the second half of the first year, an increase in interest in objects was observed in both groups, but by the end of the year the ASDs group was significantly more interested in objects than the typically developing infants. The researchers suggested that infants who later develop autism may shift their spontaneous attention mainly toward nonsocial stimuli rather than toward social stimuli, during the first year and that this early deficit in social attention might be a precursor of later impairment in joint attention. Maestro et al. (2006) reported that non-social attention was more frequent than social attention in infants who later developed ASD, regardless of whether regression was or was not part of the clinical picture. Infants with early onset of autism presented an early deficit in social attention, whereas infants with regressive autism exhibited an increase in social attention until their first birthday and a decrease in social attention after 12 months. This group (Phagava et al., 2008) also detected abnormalities in spontaneous motor activity i.e., abnormal fidgety movements in the first months of life of infants later diagnosed with ASDs in comparison to a group of typically developing infants. [Esposito, Venuti, Maestro and Muratori](#) (2009) expanded the investigation of motor activity and added another comparison group of infants later diagnosed with intellectual disability, using home videos of the first 5 months of life. Results indicated that reduced static symmetry and dynamic symmetry while lying differentiated the ASDs groups from the other comparison groups. The authors

suggest that behaviors of motor functioning in the first months of life (i.e., lower levels of symmetry) may be used as an early indicator of possible ASD.

Clifford, Young, and Williamson (2007) analyzed home videos of infants who were later diagnosed with ASDs, infants who had developmental or language delays, and typically developing infants between the ages of 12 months and 24 months. Results indicated that social behaviors such as eye contact quality, positive affect, nestling, gaze aversion, social peer interest, conventional social games, anticipatory postures and proto-declarative showing discriminated the infants who were later diagnosed with ASDs from the other two groups. The researchers suggest that between the first and second birthdays, infants with a later diagnosis of ASDs can be better distinguished from infants with developmental delays on a number of basic dyadic social behaviors rather than triadic behaviors such as joint attention and proto-declarative showing. Clifford and Dissanayake (2008) indicated that impairments in gaze and affect emerged in infants later diagnosed with ASDs as early as the first 6 months of life and impairments in joint attention were found throughout the second year of life. They suggest that abnormalities in dyadic behaviors such as poor quality of eye contact, impairment in the use of smiling and appropriate affect may be detected in home videos even before the first birthday and may play a role in later joint attention impairment.

Ozonoff et al. (2008) compared gross motor development (i.e., supine, prone, rolling, sitting, crawling and walking) and movement abnormalities of infants later diagnosed with autism (regression and no regression subgroups), infants with developmental delays and infants with typical development. Results indicated a relatively slowed motor development in all clinical groups compared to the typically developing group. More specifically, the autism (no regression) and the

developmental delay groups revealed a delay in motor development (e.g., walking, prone, and supine) compared to typically developing children. However, the autism groups (with and without regression) did not reveal elevated rates of movement abnormalities or fewer protective responses, whereas the developmental delays group displayed higher rates of movement abnormalities in sitting and prone and fewer protective responses in crawling than the other groups. The authors suggest that children with general developmental delays show the most substantial abnormalities in the rate and quality of motor development. Thus, early signs of motor delay may simply be a consequence of developmental disorder in general rather than specific to ASDs.

These data suggest that home videos of infants who later on develop ASDs reveal that these infants already manifest difficulties and impairments in communication, social relationships and sensory motor development. In the very earliest time period studied (the first 6 months of life), dyadic and intersubjective abnormalities have been detected, as well as reduced amounts of time paid to social stimuli. By the end of the first year of life a wide range of triadic early social-communicative differences are apparent (at least at a group level): reduced orienting to name; impoverished joint attention behaviors; some early motor abnormalities and reduced emotional expression. Home video studies enroll participants based on their current diagnoses and then their development is examined during younger ages prior to receiving the diagnoses. Although these earlier behaviors from a younger age distinguished children who developed ASDs later on compared to children with non-ASD diagnoses and typically developing children, we have no data regarding children who may manifest these same early behaviors during the first year or two of life but who do not develop ASDs later on. Data on children who do and do not continue to

develop ASDs later on, after showing these early markers, are required in order to specify which of these behaviors are or are not necessary and/or sufficient to be included in the prodrome/s of ASDs (the ‘specificity’ question outlined above). Some of the prospective studies which include large cohorts of both typically developing children and groups of children at risk for ASD offer some of this much needed information.

-----Table 1 about here-----

**What can we learn about the prodrome of ASDs from prospective screening studies?**

At the beginning of the 1990s, Baron-Cohen and colleagues set out to develop a prospective screening instrument for ASDs. In contrast to the rating scales available at the time that measured severity of autism symptoms but were designed to assess older clinically referred samples rather than screen a population (e.g. ABC: Autism Behavior Checklist; Krug, Arick, & Almond, 1980; CARS: Childhood Autism Rating Scale; Schopler, Reichler, DeVellis, & Daly, 1980); the intention was to develop a measure of the early, emerging signs of the disorder that would attempt to identify cases before clinically significant symptoms had been recognized by parents or professionals. Drawing on evidence that impairments in social orienting behaviors (specifically joint attention behaviors) and pretend play differentiated preschool children with ASD from children with general developmental delay (Baron-Cohen, 1987, 1993; Mundy, 1995; Sigman, 1998), a new instrument was developed. The CHAT (CHecklist for Autism in Toddlers) was designed to prospectively identify autism at 18 months of age. This age was chosen as an appropriate screen "window" (Aylward, 1997) because joint attention and pretend play typically emerge at this time in normal development. The CHAT assesses simple pretend play (appropriate use of a

tea-set, doll play, object substitution) and joint attention behaviors, pointing for interest (in combination with eye contact) and following gaze, by parental report and health practitioner observation through direct testing.

The first study tested the effectiveness of the CHAT as a screening instrument in a genetic high-risk sample of forty-one 18-month-old younger siblings of children diagnosed with autism or with ASD (Baron-Cohen, 1992; see Table 2). An often overlooked point is that this study was, in essence, the first 'high risk sibling' study of ASDs. Whilst none of 50 comparison 18 month olds failed all 5 key items, four of the children in the high-risk sibling group did so. A year later, when the children were 30 months old, a follow-up was carried out. None of the comparison children had been diagnosed with ASD. The four children in the high-risk group who had failed the five key items were diagnosed with autism.

To test whether the CHAT could prospectively identify ASD cases from a large general population, community practitioners in the South Thames region of the UK used the questionnaire with 16,235 18-month-olds as part of routine health surveillance (Baron-Cohen et al., 1996; Baird et al., 2000). On the basis of the high risk pilot it was predicted that those children who at 18 months failed all five key items would be at the greatest risk for ASD and children who failed both items measuring protodeclarative pointing (pointing for interest) would be at next greatest risk. In order to minimize false positives, a two-stage screening procedure was adopted so that screen positive children received a second administration of the screen one-month later, via a telephone follow-up. Used in this 2-stage way, the positive predictive value of the screening instrument was high (83% for ASD using the high-risk threshold). This study found that failing a combination of joint attention and pretend play items (by both parental report and health practitioner observation, and on

both administrations of the screen) indicated a significant risk for developing autism. However, sensitivity was poor (18%), indicating that four-fifths of the children subsequently identified as having ASD in the study population were missed on screening, although this improved to 38% for the one-stage screening procedure. Clinically the CHAT's sensitivity was moderate at best and the findings cannot support a recommendation for universal population screening (Baird et al., 2000). In the context of establishing the early prodromal signs of ASD, impairments at 18 months in early emerging social communication behaviors appear to characterize some but a minority only of cases who go on to have a diagnosis.

Buitelaar and colleagues in the Netherlands developed a screening instrument (ESAT: Early Screening of Autistic Traits) to identify ASD in 14-month-old children (Willemsen-Swinkels, Dietz, & van Daalen, 2006). Dietz et al. (2006) completed screening of 31,724 children at 14 months of age. Health practitioners at a well-baby clinic appointment administered an initial screen of 4 items (measuring varied play with toys, readability of emotional expression and sensory abnormalities). If a child failed 1 or more of the 4 items they were offered a follow-up home visit where a longer version of the ESAT (14 items that included many social communication items such as eye contact, response to name etc.) was administered alongside other developmental assessments. Children who failed 3 or more items of the 14-item ESAT were invited for a diagnostic evaluation at a mean age of 23 months. The ESAT did identify children with ASD ( $n = 18$ ) and also children with language disorder ( $n = 18$ ) and intellectual disability ( $n = 13$ ). The items that discriminated best between children with and without ASD were items assessing early social communication impairments, including 'shows interest in people', 'smiles directly' and 'reacts when spoken to'. This study has shown that as early as 14 months

of age some aspects of the beginnings of play; emotional responsiveness, sensory behaviors and social engagement might be present in at least some children. However, at this earlier age compared to the CHAT study (14 vs. 18 months) these early signs appear to be less specific to ASD, identifying almost as many children who went on have LD and ID. This and other studies cannot report on the sensitivity of these signs to all cases of ASD until a population follow up of the whole sample has been conducted to identify missed cases.

A number of other groups have also developed and begun to test screens for ASDs both in total population samples and in clinically referred samples. Robins et al. (2001) developed a modified version of the CHAT (the M-CHAT) that included additional items measuring other aspects of early social communication impairments characteristic of autism (e.g. response to name, imitation) as well as repetitive behaviors (e.g. unusual fingers mannerisms) and sensory abnormalities (e.g. oversensitivity to noise). The M-CHAT is a parent report instrument and the health practitioner does no direct testing. In their initial report, Robins et al. (2001) had tested 1,122 unselected children (initially at 18 months but subsequently at 24 months of age) and 171 children referred for early intervention services (considered to be at high risk of having an ASD or other developmental disability). The screen (initially with 30 items, subsequently reduced to 23 items) was completed independently by parents of children seen by pediatricians in the unselected sample and seen by early intervention service providers in the referred sample. Following analysis of the first 600 returns, a cut-off was set as failing 2 from 8 'critical items' or any 3 items from the total of 23 items (Robins et al., 2001). Once a child failed the M-CHAT the research team re-administered the screen by telephone and if a child still scored above cut-off the family was invited for an assessment.

Of the 58 children who failed on both administrations of the M-CHAT, 39 subsequently received an ASD diagnosis and the remaining 19 were found to have language or global developmental delay. Note that only 3 of the 39 children with ASD were from the unselected population, with the majority being identified from the sample referred for early intervention services. Robins et al. (2001) found that the items that best discriminated between children with ASD and children with other developmental problems were those that measured joint attention behaviors (pointing and following a point, bringing things to show), social relatedness (interest in other children, imitation) and communication (response to name). Robins et al. (2001) calculated sensitivity, specificity and positive predictive values for various combinations of M-CHAT items and demonstrated that in this largely referred sample its instrument parameters were strong. A recent study (Kleinman et al., 2008) has reported on the M-CHAT with a new sample of 3,793 children aged 16 to 30 months. Kleinman and colleagues found a positive predictive value of 0.36 for the initial screening which improved to 0.74 for the screening plus the follow-up telephone interview. Again, most cases were identified from the 'high risk' sample of children referred for early intervention services or due to a developmental concern. Follow-up studies will allow us to estimate the instrument's parameters when used on an unselected population, in particular its sensitivity in detecting cases of ASDs in children about whom there had not been previous developmental concerns which would constitute a better test of prodromal signs, as opposed to early emerging (and recognized) signs of the disorder itself.

Wetherby and colleagues (Wetherby, Brosnan-Maddox, Peace, & Newton, 2008; Wetherby et al., 2004) have also developed an early screening tool that can be used from 6 to 24 months of age – the Infant Toddler Checklist (ITC). The ITC is a

broader developmental screen that successfully identifies children with developmental delay as well as children with an ASD. In their most recent work, they have shown that it is possible to prospectively identify towards the end of the first year of life children who will go on to have a diagnosis of an ASD (Wetherby et al., 2008). This is a goal that is shared by others who have developed instruments targeted at signs identifiable before the end of the first year of life, although these remain to be fully tested for their ability to prospectively identify ASDs at this age.

The First Year Inventory (FYI; Reznick, Baranek, Reavis, Watson, & Crais, 2007; Watson et al., 2007) is a questionnaire administered to infants' caregivers to identify 12-month-olds in the general population who are at risk for atypical development in general, but with a special focus on infants whose risk patterns are most predictive of a future ASDs. The target behaviors depicted by the various items are based on retrospective and prospective studies that suggested risk markers in infancy for an eventual diagnosis of ASD. In this 63-item checklist, parents are asked to describe their children on two major domains of social and communicative behaviors (i.e., social orienting, receptive communication, social affective engagement, imitation, and expressive communication) and on sensory and regulatory behaviors (i.e., sensory processing, regulatory patterns, reactivity, and repetitive behavior). A retrospective version of the FYI was administered to parents of preschool children with ASD, children with other developmental disabilities, and children with typical development, to strengthen the validity of the FYI and to improve its utility for prospective screening of 12-month-olds both for infants from the general population and infants at risk (Watson et al., 2007). Altogether findings indicated that children at risk scored higher on the Social-Communication domain than on the Sensory-Regulatory domain.

Overall these screening studies have shown that it is possible to prospectively identify ASD, including in children about whom parents and professionals did not have pre-existing concerns, from the age of 18 and even 14 months of age. The most common early signs captured by the screen are impairments or delays in early emerging social communication behaviors such as response to name, joint attention and play behaviors; although at least in the Netherlands study there was a suggestion that sensory abnormalities or a restricted repertoire of play activities might also be early indicators of later ASD. However, in none of the studies that have included systematic follow-up of the screened populations to identify all cases at outcome have the signs been universal. Scientifically such signs are promising but neither universal nor necessarily specific markers of a later emerging ASD presentation (as opposed to other neurodevelopmental disorders). Therefore, one needs to be cautious about recommending universal screening.

-----Table 2 about here-----

### **What can we learn about the prodrome of ASDs from prospective studies of younger siblings?**

As autism is amongst the most heritable of neurodevelopmental conditions, it may have been assumed that autism would allow for one of the strongest tests of our ability to identify risk factors and prodrome status and thus to test neurodevelopmental theories regarding its underpinnings and influences, as well as the effectiveness of preventative interventions. Furthermore, autism is one of the earliest emerging neurodevelopmental conditions, with DSM-IV (1994) and ICD-10 (1993) requiring abnormality to be evident in the first 3 years of life to meet diagnostic criteria for the 'core' disorder of childhood autism (ICD-10)/autistic disorder (DSM-IV). Whilst some children, particularly some of those with average or

above average IQ (including those who would meet criteria for Asperger syndrome), diagnosis does not occur until school age or even older; it is now common in many countries for autism to be diagnosed by the age of two or three (Charman & Baird, 2002; Charwaska, Klin, Paul, Macari, & Volkmar, 2009; Mandell, Novak, & Zubritsky, 2005). This means that, in combination with the high recurrence rate in siblings, younger siblings of children with a diagnosis can be studied from a young age, including from birth and potentially even during pregnancy.

This has led to considerable interest and research activity internationally to study cohorts of 'at risk' younger siblings of children with a diagnosis from the first years of life. This contrasts to many other disorders in this special issue in which high risk genetic designs involve following offspring (sometimes as young as infancy) of parents diagnosed in adulthood (e.g. Bipolar disorder: Chang, et al., 2003; Psychosis: Schubert & McNeil, 2004; Schizophrenia: Bota, Sagduyu, Filin, Bota, & Munro, 2008). However, there are exceptions including studying younger siblings of children with ADHD (Faraone, Biederman, Mennin, & Russell, 1998) and dyslexia (Carroll & Snowling, 2004). In this section we review studies of younger siblings of children with autism and their contribution to our knowledge regarding the early markers and prodrome of ASD.

Many investigators are currently conducting prospective longitudinal studies of younger siblings of children with ASDs who as a group are at higher risk to develop an ASD compared to the general population (for a summary; see Table 3). The majority of literature regarding the developmental trajectories of these younger siblings reports on the early development of younger siblings as a group without reference to later diagnoses. Therefore these data do not necessarily pertain to our discussion of the prodrome because, whilst these groups of siblings include siblings

who will later on be diagnosed with ASD, they also include other siblings who will be diagnosed with other disorders, or with no disorder at all (for summaries; see Rogers, 2009; Yirmiya & Ozonoff, 2007; Zwaigenbaum et al., 2009; Zwaigenbaum & Stone, 2008). Therefore, inconsistent findings emerging from these studies are most likely due to differences in proportions of participants who will later on be assigned to the ASD versus other diagnoses versus typically developing groups, and cannot reliably teach us about the prodrome of autism. Even the often made assumption that these studies inform us about the broad autism phenotype may be questionable because significant differences between the full group of younger siblings of children with autism and the comparison group may (or may not) be due to the siblings who will later on be assigned to the ASD group. The point is, without follow-up information on outcome we do not yet know if such early indicators are ‘prodromal’ signs of ASD or not.

However, such studies do raise some intriguing scientific questions about the developmental trajectories that might be seen in ‘high risk’ siblings, including some preliminary evidence of disrupted neural processing of both social and non-social stimuli that may be indicative of neural endophenotypes of ASD (Elsabbagh et al., 2009; McCleery, Allman, Carver, & Dobkins, 2007; McCleery, Akshoomoff, Dobkins & Carver, in press). They also highlight the intriguing possibility that some at risk siblings might show early perturbations (perhaps contributing to the group-level differences found compared to siblings of typically developing children) but not go on to develop ASDs. This ‘recovery’ pattern of development might inform us about developmental brain plasticity and developmental trajectories, and potentially both genetic and environmental effects on these processes (Elsabbagh & Johnson, 2007; Rogers, 2009).

So, in relation to identifying the ASD prodrome, siblings studies are most valuable when early developmental data is associated with outcome diagnoses, and even then there may be some inaccuracies as these outcome data are reported for ages 2 and 3 years and may not include children who will fulfill criteria for diagnoses such as Asperger syndrome only later on. Thus, in the context of our discussion of the prodrome of ASD, we will limit our discussion to the few studies that report on early development and markers as associated with a later diagnosis of an ASD.

To date, only four groups report on associations among early development during the first year or two of life and later diagnoses of ASDs. Working in Canada, Zwaigenbaum and his group were the first to publish longitudinal findings regarding the early markers for ASD. Zwaigenbaum et al. (2005) examined the development of high risk (SIBS-A) and low risk infants from 6 to 24 months and identified several behavioral markers at 12 months (but not at 6 months) that predicted later diagnoses of ASD at 24 months. The identified risk markers included atypical eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, reactivity, social interest, and sensory-oriented behaviors. Siblings diagnosed with ASD at 24 months also exhibited temperament characteristics of decreased activity at 6 months, intense distress reactions and a tendency to fixate on objects at 12 months, as well as early language delays at 12 months. Mitchell et al. (2006) added that siblings diagnosed with ASD at 24 months in this sample had delays in gestural communication (i.e., giving, pointing, nodding head) as reported by their parents at 12 months. Bryson et al. (2007) documented a case series of 9 siblings from the previous cohort who were followed prospectively from 6 months to 36 months, and who were diagnosed with ASD between age 24 months and age 36 months. In this report, 2 subgroups of children with distinguishable early developmental profiles were

identified: The first subgroup (6 siblings) displayed a decrease in IQ from average functioning to severe cognitive impairment (up to 41 points) between 12 months and 36 months. The second subgroup (3 siblings) continued to obtain average or near average scores from 12 months to 36 months. The emergence of ASD in all siblings was associated with a distinct temperament profile characterized by marked irritability, intolerance of intrusions, proneness to distress/negative affect, and difficulties with self- or other-regulation of state.

This group of researchers (Loh et al., 2007) examined the stereotypic movements and postures that occurred during standardized observational assessments at 12 and 18 months and reported that SIBS-A who were later diagnosed with ASD waved their arms more frequently than the non-ASD siblings and control groups at both ages. More recently, Brian et al. (2008) examined the best behavioral markers of ASD at age 18 month as derived from early measures (the ADOS: Autism diagnostic observation schedule; Lord, Rutter, DiLavore, & Risi, 2002 and the AOSI: Autism Observational Scale for Infants; Bryson, Zwaigenbaum, McDermott, Rombough, & Brian, 2008) that contributed to the identification of ASD at 36 months. Most of the best discriminators of later ASD emerged from the ADOS social and behavioral domains (e.g., quality of social overtures, directed facial expression, repetitive interests, hand and finger mannerisms, and sensory interests) as well as two non-verbal items (i.e., pointing and gestures) from the ADOS communication domain. Furthermore, the AOSI analysis included temperamental characteristics and difficulties in motor control and/or coordination that were also best discriminators of later ASD. In sum, this group of investigators emphasize the importance of dimensions of temperament (i.e., state regulation, motor control and coordination), as well as social-communication deficits when assessing toddlers for possible ASD.

More specifically, they emphasized that although more SIBS-A than SIBS-TD had difficulties with transitions, 'difficulty with transitions' should be considered a potential risk marker and evaluated only in combination with other risk markers for ASD.

Rebecca Landa and her group are also among the first investigators who initiated a prospective study of 6-month old infants SIBS-A and infants with no family history of autism. At 24 months, participants were classified into an ASD group, LD (language delayed) group, and an unaffected group. The ASD group had the slowest developmental trajectory, with a significant decrease in development between 14 and 24 months. Whereas at age 6 months, no significant differences emerged among the three groups on the Mullen Scales of Early Learning (MSEL; Mullen, 1995), at 14 months the ASD group performed significantly poorer than the unaffected group on the MSEL domains with the exception of Visual Reception domain. By 24 months, the ASD group performed significantly poorer than the unaffected group on all the MSEL scales and significantly poorer than the LD group on the Gross and Fine Motor and Receptive Language scales (Landa & Garrett-Mayer, 2006). In their next report, Landa, Holman and Garrett-Mayer (2007) further extended their report on the social and communication development of the SIBS-A and siblings with no family history of autism. This time, participants were classified into the following groups at 30 or 36 months: ASD group (with two subgroup of early/late diagnosis), BAP group, and non-BAP group. Results indicated that the siblings in the ASD early diagnosis subgroup differed at ages of 14 and 24 months from all other groups, in their communication and play behavior, as measured by the Communication and Symbolic Behavior Scale – Developmental Profile (CSBS-DP; Wetherby, Allen, Cleary, Kublin, & Goldstein, 2002). Similar to their previous

findings, the developmental trajectories of these groups revealed delayed social and communication development for the ASD group between 14 and 24 months. Landa and colleagues also identified different developmental trajectories in the subgroup who received an early diagnosis (a working diagnosis at the 14 month assessment) and those who received a diagnosis at the later 24 month assessment. For this latter group, some skills continued to grow but at a slow rate between the two time points, others plateaued, whilst others decreased (shared positive affect and gestures). This would be consistent with the commonly (retrospectively) reported phenomenon of regression or loss of skills and is taken up later on in this review. Sullivan et al. (2007) continued this line of research by examining the behavior of response to joint attention at 14 and 24 months in this cohort of high- and low-risk siblings. Results indicated that at 14 months the ASD and BAP groups were indistinguishable from each other and performed less well on several joint attention tasks than the non BAP group. However by 24 months the ASD group performed less well on the joint attention tasks than both the BAP and non BAP groups. Furthermore, joint attention skills at age 14 months predicted both language ability and the outcome diagnosis of ASD.

Working in California, Sally Ozonoff, Sally Rogers and Marian Sigman are conducting a large scale prospective study of siblings of children with autism. Nadig et al. (2007) reported that at age 6 months, no significant differences were found between SIBS-A and SIBS-TD in their orienting to their name calling. However, at age 12 months all SIBS-TD (100%) oriented on the first or second call of their name compared to 86% of the SIBS-A. Furthermore, 75% ( $n = 9$ ) of the SIBS-A who failed to respond to their name being called at age 12 months were identified at age 24 months with ASD ( $n = 5$ ) or with other developmental delays ( $n = 4$ ). Thus, these

authors conclude that decreased response to name at age 12 months has a high specificity for 24-month outcomes of ASD (0.89) and for any type of developmental delay (0.94). However, sensitivity was much lower (0.50 for ASD; 0.39 for all types of delay). In their next report, Merin, Young, Ozonoff and Rogers (2007) tested the 6-month-old SIBS-A and SIBS-TD during the Still Face paradigm and examined their visual fixation patterns and affective displays using sophisticated eye tracking procedures. A subgroup of 11 infants demonstrated diminished gaze to the mother's eyes relative to her mouth during the Still Face episode. Interestingly, 10 of the 11 infants characterized by this pattern were SIBS-A. No significant differences emerged between the two groups in affective displays (i.e., smiling, negative affect), in the total amount of fixation time, or in the fixation directed at the face versus other areas. Yet in their follow-up study, Young, Merin, Rogers, and Ozonoff (2009) examined the predictive utility of these gaze and affective behaviors at 6 months to diagnostic outcome data at age 24 months, and surprisingly report that none of the infants who demonstrated diminished gaze to the mother's eyes relative to her mouth at 6 months, had any signs of autism at the outcome assessment at 24 months. Moreover, all three children who were diagnosed with autism at 24 months (2 SIBS-A and 1 SIBS-TD) demonstrated consistent eye contact and typical affective responses at 6 months during the Still face procedure. Similarly, no associations were found between face scanning and affective responses at 6 months and the continuous measures of autism symptom frequency or symptom severity, e.g., ADOS and the M-CHAT scores at 24 months. Yet growth curve analyses revealed significant associations between face scanning and expressive language: diminished gaze to the mother's eyes relative to her mouth at 6 months predicted higher scores of expressive language at 24 months as well as greater rates of growth. The authors conclude that gaze behavior is not a

specific early marker for autism but rather that gaze to the mouth may play an important role in language development.

Next, Ozonoff et al. (2008) examined behaviors of atypical object exploration (with novel play materials) at 12 months as a predictor of subsequent ASD diagnosis in this sample in which participants were classified into three groups according to their outcome diagnoses at 24 and 36 months: Autism/ASD group, other delays group and no concern group. The Autism/ASD group was distinguished from the other two groups by increased frequency of spinning, rolling and rotating the objects, and by unusually prolonged visual inspection, often associated with atypical features such as examining the object from odd angles. Furthermore, repetitive behaviors at 12 months were significantly associated with cognitive and symptomatic status at the 36 month outcome, yet some infants who showed these behaviors did not receive an ASD diagnosis later on. These results suggest that repetitive or stereotyped behaviors are early risk markers in the development of some but not all children with ASD.

Finally, also using growth curve analyses, Yoder, Stone, Walden and Malesa (2009) examined the contribution of initial values and growth rates of two early social skills, i.e., weighted triadic communication and responding to joint attention in predicting later ASD in a group of SIBS-A followed from 15 to 34 months of age. Results indicated that both predictors (weighted triadic communication and responding to joint attention) as well as initial language age were associated with later ASD diagnosis.

Altogether these studies corroborate findings from the home video and screening studies in that various behavioral indices of attention, perception, communication, temperament, social behavior and sensory-motor development characterize children who later on develop ASDs. Yet no one developmental

trajectory of a prodrome has been identified. To date, most of these high risk sibling studies have examined the extent to which isolated behavioral abnormalities map onto an ASD 'outcome'. In future work groups will likely begin to examine whether *combinations* of abnormalities, for example those at risk siblings showing impairments on both social (eye gaze; orienting to name) and non-social (motor, attentional control) measures, might be better predictors of developing an ASD, and thus constitute a kind of 'cumulative risk' ASD prodrome or marker.

-----Table 3 about here-----

### **Brain development and the prodrome of ASD**

There is also considerable interest in identifying structural neuroanatomical associations of ASD, in particular those that might characterize individuals at risk of development ASD before the onset of frank diagnostic symptoms. One candidate has emerged over the past 5 years that of enlarged brain size; in particular a number of lines of evidence that brain growth trajectory might be abnormal in early development.

There had been long recognition that increased brain size (often assumed on the basis of head circumference measurements; an assumption that has empirical validity (Hazlett et al., 2005)) was more common than expected in clinical samples of children and adults with ASD; with rates of macrocephaly (head size greater than 2 standard deviations above the norm) in the range of 15%-30% (Bailey et al., 1995; Bolton et al., 1994; Davidovitch, Patterson, & Gartside, 1996; Woodhouse et al., 1996; see Lainhart, 2006, for a review). However, head circumference and magnetic resonance imaging studies find stronger associations in children than in adults and macrocephaly has not been found in all samples (Redcay & Courchesne, 2005). A notable study by Courshene et al. (2003) found that head circumference was smaller

than population norms at birth but there was accelerated growth such that by age 6-14 months with 53% of the sample revealing macrocephaly. Furthermore, in this small case series enlarged head circumference was positively associated with measures of autism symptom severity.

A number of subsequent reports broadly confirmed the finding of accelerated head growth during the first year (though not the finding of abnormally small head size at birth) with a subsequent decline in trajectory from the 2<sup>nd</sup> year of life (Dawson et al., 2007; Dementieva et al., 2005; Fukumoto et al., 2008; Hazlett et al., 2005). A number of structural imaging studies have also found increased brain volume or increases in specific brain structure in 2 to 4 year children with ASD (Aylward, Minshew, Field, Sparks, & Singh, 2002; Courchesne et al., 2001; Hazlett et al., 2005; Sparks et al., 2002). Two reports of head circumference in sibling studies have found an association between enlarged head circumference or head circumference growth rate and early emerging symptoms (Elder, Dawson, Toth, Fein, & Munson, 2008) or initial ASD diagnosis at 24 months (Zwaigenbaum et al., 2008). However, in the only study to examine whether head circumference growth differed between children with and without a history of regression, no differences were found (Webb et al., 2007).

A note of caution is warranted since other studies have not replicated the finding of increased trajectory of head circumference in the first year (Torrey, Dhavale, Lawlor, & Yolken, 2004; van Daalen, Swinkels, Dietz, van Engeland, & Buitelaar, 2007), and in some studies body length and weight also showed differences from population norms. Another caution is that we do not know yet how many children undergo this abnormal brain growth trajectory as most studies have analyzed differences only in terms of groups, so suggestions that measurement of head

circumference might contribute to clinical surveillance needs to be interpreted with caution.

However, this finding has attracted enormous interest in the idea that a trajectory of abnormal brain growth that occurs pre-symptomatically might be a marker of underlying neurodevelopmental disturbances that contribute (or at least 'signpost') the later emergence of the autism phenotype. The window of this abnormal brain growth coincides with the period of Synaptogenesis and subsequent pruning when cortical connections are developed, refined and stabilized. This process is interactive with the infant's experience of the environment, a process that Greenough et al. (1987) termed 'experience expectant development', and the consequences of a developing brain whose connections are not undergoing the usual refinement on information processing may result in a secondary pathogenic process that impacts on future development in the process of the emergence of the ASD phenotype.

A recent study identified an intriguing finding that might be related to this overall pattern of abnormal brain growth. Mosconi et al. (2009) found that by the age of 2 years children with autism had enlarged amygdalae, particularly in the right hemisphere over and above an increase in total brain volume and that this increase maintained (but did not increase further) up until the age of 4 years. This indicates that prior to this age brain growth in this particular structure is likely to have been abnormal. Furthermore, amygdala volume at age 4 was positively associated with joint attention skills at the same age. Joint attention behaviors involve co-ordination (initiating, response) between objects and caregivers or other adults; often involving the shifting of gaze to and from the gaze of the adult. It is well-established that the amygdala is recruited in facial emotional recognition tasks and in particular in

orientation to the eye region (Adolphs et al., 2005) and that children and adolescents with autism show abnormal functional MRI responses to such tasks (e.g. Dalton et al., 2005; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004; Wang et al., 2005) and that young children with autism show enlarged amygdale (Sparks et al., 2002).

In their discussion Mosconi et al. (2009) build on earlier accounts by Baron-Cohen (Baron-Cohen et al., 1999) and Schultz (2006) whereby abnormal amygdala responses during social processing (including in such activities as eye contact and joint attention) leads to a cascade of neurodevelopmental outcomes, raising the possibility that infants and young children with autism find less intrinsic reward in the typical social affective interactions with caregivers and other adults (see also Dawson et al., 2004). The precedence of abnormal behavioral responses (not looking to the eyes) versus abnormal brain structure of function (enlarged and atypically responsive amygdalae) is not known but such hypotheses establish specific brain systems as potential neuroanatomical and neurofunctional prodromal markers of ASD, in this case from at least 2 years of age but possibly from much earlier in development.

This period of abnormal trajectory of brain growth and possibly cortical connectivity resonates with a number of clinical, neuroanatomical and neurofunctional findings. With respect to the latter, the interest in an abnormal head/brain growth trajectories leading to abnormal cortical organization also chimes with the current interest from functional MRI studies that have found abnormality connectivity – with reduced connectivity between distal brain circuits and increased connectivity between proximal brain circuits on a wide number of cognitive tasks (Just, Cherkassky, Keller, Kana, & Minshew, 2007; Just, Newman, Keller, McEleney, & Carpenter, 2004; Kana, Keller, Minshew, & Just, 2007; Koshino et al., 2008; Minshew & Williams, 2007). These observations and experiments, largely conducted

with samples of older children and adults, might however be consistent with continuity in organization of the cortical system from early infancy throughout childhood development – identifying at least a possible candidate neuropathological process, even its cause is not yet known. Whether such neuropathological processes will ever be seen as reliable and universal enough in relation to ASD outcomes to be candidate prodromal signs will require a considerable body of further research. Furthermore, the degree to which any of these possible brain markers (abnormal connectivity; abnormal growth trajectory) will be specific to ASDs is unclear as they are also emerging as putative biomarkers in relation to many other neurodevelopmental and neuropsychiatric outcomes (e.g. ADHD: Castellanos et al., 2002; Schizophrenia: Bluhm et al., 2009) and their specificity to ASD has not yet been adequately tested. However, the notion that a neurodevelopmental perturbation might herald and precede the emergence of symptoms of ASD resonates at behavioral level with the long-recognized phenomenon of developmental regression or ‘setback’.

### **Is regression part of the prodrome in ASDs?**

According to studies reliant on retrospective parental report, regression or loss of skills is seen in between 15% and 30% of cases in different clinical and population samples with the most common timing being between 12 and 24 months of age (Baird et al., 2008; Fombonne & Chakrabarti, 2001; Lord, Shulman, & DiLavore, 2004; Luyster et al., 2005; Richler et al., 2006; see Young & Ozonoff, in press, for a review). This is also around the time that the earliest symptoms of ASD emerge in many children and both the retrospective videotape analysis studies (e.g., Werner & Dawson, 2005) and the ‘at risk’ sibling studies (Landa & Garrett-Mayer, 2006; Landa et al., 2007) reviewed above have shown prospective evidence of loss of skills or stasis. The speculation surrounding whether there may be a link between the apparent

pattern of abnormal brain growth and the phenomenon of regression whose timing soon follows on (though it has yet to be established whether this is true for individual children) is easy to understand.

The phenomenon of regression is yet not well understood. Some parents report a very abrupt change in their child's development, most notably when early language skills are lost. Others report a much more gradual change over several months. There is increasing recognition that social skills and interest, play skills and sometimes (though more rarely) motor skills can also be lost or plateau (Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Ozonoff, Williams, & Landa, 2005; Werner & Dawson, 2005). In addition it is also now understood that some children may lose language skills that are not a firmly embedded as the currently widely used definitions from the ADI-R (Lord, Rutter, & Le Couteur, 1994) 'loss of 5 words used communicatively for at least 3 months'), that Baird et al. (2008) characterized as 'lower level regression'. Ozonoff and colleagues (Hansen et al., 2008; Young & Ozonoff, in press) have reviewed the evidence for whether pre-regression development was clearly typical and the children were asymptomatic and concluded that this is not the case. In fact children can show the full range of patterns with some children showing early symptoms before their 1<sup>st</sup> birthday and then losing skills whilst others show no early signs but then undergo a regression (Young & Ozonoff, in press). Across studies there is variability in the extent to which regression is associated with poorer outcomes in terms of IQ, adaptive behavior or symptom severity or even associated medical conditions such as gastro intestinal symptoms (e.g. contrast the findings of Baird et al., 2008; Richler et al., 2006). Only in a minority of cases is regression associated with the onset of seizures (Shinnar et al., 2001; Tuchman & Rapin, 1997).

A growing body of research suggests different onset patterns for children with ASDs with and without developmental regression (for a review see Ozonoff, Heung, Byrd, Hansen, & Hertz-Picciotto, 2008). Furthermore, fixation or developmental stagnation/plateau (Hansen et al., 2008; Siperstein & Volkmar, 2004) and/or regression may appear following typical development or after a period of time in which some risk markers (e.g., language delay) were already apparent. It appears that developmental stagnation/plateau and/or regression in any developmental domain associated with ASDs such as a loss in communication skills, social skills, motor, play, self-help or in any other developmental domain may play a part in the prodrome of some but not all children who later on develop ASDs.

When evident, it appears that regression may follow a year or two of typical development or an earlier period of some other developmental concerns and difficulties (De Giacomo & Fombonne, 1998; Fombonne & Chakrabarti, 2001; Goldberg et al., 2003; Kurita, 1985; Lingam et al., 2003; Ozonoff et al., 2008; Ozonoff et al., 2005; Richler et al., 2006). Goldberg et al. (2003) and Hansen et al. (2008) report that the majority of children who experience regression show regression in social and language abilities jointly or in social abilities only. A minority of children reveal regression only in language abilities with non-significant differences in the clinical picture among children with regression in language abilities versus those with regression in other domains (Luyster et al., 2005). Ozonoff et al. (2008) conclude their review by suggesting that the onset of ASDs may be marked by the two extremes of development with no evidence of regression on one end of the continuum and regression on the other end of the continuum, and intermediate manifestations of stagnation/fixation and developmental difficulties and small losses prior to the full blown clinical picture of ASDs. This conclusion once more

emphasizes the notion that whilst regression may be part of the prodrome and the clinical picture for children with ASDs it will not be a universal one. One note of caution, however, is that although there is at least one example from the prospective high risk sibling studies where a subgroup of children who went on to have ASDs lost skills in the second year of life (Landa et al., 2007), most studies have not yet provided prospective data on the regression phenomenon (though see Ozonoff et al., in press; for an exception where loss of skills was common in a group with an ASD outcome). It also appears that objective observations and parental reporting of regression or setback do not always concur (see Ozonoff et al., 2008, in press; for discussion).

However, regression remains intriguing as a candidate prodromal feature of ASD because, aside from later occurring childhood disintegration disorder (CDD) where regression occurs after the age of 2 years or even later following clearly typical development (regression in autism is before this age commonly between 12 and 20 months of age) (Volkmar & Cohen, 1989) or Landau-Kleffner syndrome that is due to localized peri-sylvian epilepsy (Robinson, Baird, Robinson, & Simonoff, 2001), it appears to be relatively specific to more narrowly defined autism. A recent report examined how common regression was in children with specific language impairment (SLI), also called developmental language disorder (DLD). Pickles et al. (2009) found that regression occurred in only 1% of children with SLI compared to 15% of children with autism or a broader ASD. In a related study the same group reported that regression occurred in 30% of children with narrowly defined autism (children meeting ICD-10 criteria for childhood autism plus the autism threshold on the ADI-R and ADOS), 8% of children with broader ASD/PDD and only 3% of controls with a mixture of intellectual, learning and behavioral difficulties (Baird et al., 2008).

Pickles et al. found a strong association between age of first words and likelihood of undergoing regression. That is, frank loss of language skills was associated with switching from the most advanced early language to being amongst the slowest (in terms of eventual onset of phrase speech). They conclude that regression might be more common than currently recognized; with whatever neurodevelopmental perturbation that is occurring being unrecognized by parental observation. However, the challenge would then be to understand what the nature and causes of the underlying perturbation in these cases is. In common with most others investigating regression, this study relied on retrospective parental report many years after the phenomenon of investigation; limiting our confidence to draw strong conclusions from these data until they are corroborated (or not) in prospective studies.

In addition to our discussion of retrospective and prospective studies pertaining to behavioral and biological early markers that may be associated with the prodrome/s of ASD we now move on to discuss issues related to perinatal developments and genetics as these contribute to risk and vulnerability to develop ASDs.

### **Perinatal Risk Factors**

Although the genetic basis for ASDs is supported by various genetic studies (Bailey et al., 1995; Gupta & State, 2007; Muhle, Trentacoste, & Rapin, 2004; Risch et al., 1999), current estimates of ASD prevalence are 1 in 100 to 1 in 150 (Baird et al., 2006; CDC, 2007), indicating that the prevalence of autism and related ASD is substantially greater than previously recognized. Thus, it has been suggested that one or more environmental triggers may be contributors (Bello, 2007). It is reasonable to assume that both environmental and heritable factors contribute risk to ASD and there is increasing recognition that environment in addition to genes needs to be considered

in genetic studies pertaining to risk and vulnerability to ASD. Environmental factors, especially the in utero milieu, likely modulate genetic vulnerabilities responsible for the manifestation of ASD in individual children. Two seminal studies by Caspi and his colleagues illustrated the importance of environmental as well as genetic information in understanding human behavior. In one study, on a sample of male children, they found that maltreated children with a genotype conferring high levels of a neurotransmitter-metabolizing-enzyme (MAO-A) expression were less likely to develop antisocial problems. These findings may partly explain why not all victims of maltreatment grow up to victimize others, and they provide epidemiological evidence that genotypes can moderate children's sensitivity to environmental insults (Caspi et al., 2002). In a second prospective-longitudinal study of a representative birth cohort, they tested why stressful experiences lead to depression in some people but not in others. In this study, differences in the serotonin transporter (5-HTT) gene were found to moderate the influence of stressful life events on depression, thus demonstrating a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup (Caspi, et al., 2003). However, Risch et al. (2009) questioned this finding in a recent meta-analysis in which no associations were found between serotonin transporter genotype alone or in interaction with stressful life events on the one hand, and elevated risk for depression, on the other hand. Yet, since ASD is a developmental disorder characterized by early onset, a likely target for environmental risk, and interacting with genotype, are the pre-natal and peri-natal periods.

In 1992, Hales and Barker highlighted the existence of associations between early growth patterns and chronic adult diseases. They proposed the 'fetal programming' concept, that describes fetus' physiological adaptation to characteristics of the

intrauterine environment in which it is developing. When the fetal environment is deprived of nutrients, an adaptive change occurs, with optimization of the growth of key body organs at the expense of other organs (Hales & Barker, 1992). This adaptation involves changes in the epigenetic ('epi': *on* the gene) program and has long-term consequences (Gicquel, El-Osta, & Le Bouc, 2008). Epigenetics relates to stable and heritable patterns of gene expression that do not involve changes in DNA sequence. Epigenetic mechanisms manage gene expression and are required to achieve the stable repression or expression of genes at defined developmental stages. Prenatal and perinatal environmental challenges during the course of pregnancy are likely causes of deleterious epigenetic modifications to the fetal brain with long-term developmental consequences, including risk and vulnerability to ASD. Moreover, there is increasing evidence that prenatal psychological stressors program fetal and neonate Hypothalamus-Pituitary-Adrenal (HPA) axis reactivity with long-term effects on future development, and investigators have been identifying the epigenetic machinery mediating the impact of prenatal stressors on the child development (McGill et al., 2006; Weaver et al., 2004). Fetal programming involving epigenetic changes might be a mediating mechanism between prenatal risk factors and subsequent developmental outcome.

Recent investigations focused attention on the crucial prenatal and perinatal periods and identified potential risk factors for ASD (Gillberg & Cederlund, 2005; Glasson et al., 2004; Kinney, Munir, Crowley, & Miller, 2008; Kolevzon, Gross, & Reichenberg, 2007; Larsson et al., 2005; Maimburg & Vaeth, 2006; Williams, Helmer, Duncan, Peat, & Mellis, 2008). Croen, Grether and Selvin (2002) investigated a total population of more than 3.5 million live births from 1989-1994 in California. Participants included 4356 children known to the state as diagnosed with full

syndrome autism (children with Asperger's disorder as well as other PDD disorders were not included in the study) and 3,497,870 live births as comparisons. The following data were retrieved from the live birth certificate electronic files: sex of the child, birth weight, plurality, birth order, maternal age at delivery, race/ethnicity, birth place, and current level of education. The findings indicated that among child characteristics there is an increased risk for autism in males, in multiple births (but Piven et al. (1993), reported equal distribution for probands with autism and siblings), and that relative to 1<sup>st</sup> born children, third and later-born children are at a reduced risk, but no association was found with low birth weight. Among maternal characteristics older age and higher educational level involved higher risk with women over the age of 35 at a significantly higher risk than women under 20 years of age, and women with a post-doctorate education at significantly higher risk than women with less than high-school education. In addition, Afro-American women were found to be at a higher risk to have a child with autism compared to other ethnic groups. Yet although it is a total population study in that all live births were potentially included, as the authors state, the study is not an epidemiological study because some children may be undiagnosed whereas other children diagnosed or undiagnosed, may not have been enrolled in the state operated services through which the participating children with autism were identified. To the extent that some self selection processes involved in receiving the diagnosis and/or services are operative, the data may be biased. Nonetheless, this is a unique study due to the huge number of participants with autism, use of total live births as a comparison group, data retrieved from medical files rather than from possibly biased parental recall, and the fact that each characteristic was estimated in association with other characteristics. Similar studies conducted in Denmark, Australia, Sweden and Israel also suggest that maternal

smoking, low Apgar scores at 1 and 5 minutes, gestational age at birth of less than 35 weeks, older parental age, and maternal psychiatric status of a past or current psychiatric diagnosis as well as labor complications increase the risk rate for autism (Glasson et al., 2004; Hultman, Sparén, & Cnattingius, 2002; Larsson et al., 2005; Lauritsen, Pedersen, & Mortensen, 2005; Reichenberg et al., 2006).

Kolevzon et al. (2007) reviewed 7 independent investigations which all involved large populations and identified parental age and obstetric conditions as risk factors. Included in obstetric conditions are (1) low birth weight (LBW) and duration of gestation and (2) intrapartum (during labor and delivery) hypoxia and fetal hypoxia. Several obstetric variables may act as proxies of fetal hypoxia, including low Apgar score, fetal distress, cesarean delivery, threatened abortion, and bleeding during pregnancy. These conditions are mostly present in preterm babies and therefore in the next section we specifically address premature birth as associated with ASD.

Low birth weight is of special interest because it is accurately measured and associated with a range of cognitive deficits and psychiatric outcomes, including problems related to speech and language, internalizing behavior problems, attention, social skills, hyperactivity, and learning disabilities. There is also a substantial literature base on the relationship between LBW and lower intelligence (Casey, Whiteside-Mansell, Barrett, Bradley, & Gargus, 2006). Prematurity and low birth weight have been identified in numerous studies as a risk factor for ASD (Eaton, Mortensen, Thomsen, & Frydenberg, 2001; Hultman, Sparen, & Cnattingius, 2002; Larsson et al., 2005; Schendel & Bhasin, 2008; Williams et al., 2008). In a recent study, parental reports on Extremely Low Birth Weight (ELBW) children were compared to those of matched normal weight children with findings suggesting an increase in symptoms pertaining to Autistic and Asperger's disorders at school age (as

well as ADHD and anxiety) in the ELBW group (Hack et al., 2009). Limperopoulos et al. (2008) further underscore the risks conferred by preterm birth. In this study of 91 extremely preterm infants, 26% fell above the cutoff score on the M-CHAT at the age of 18 months. Positive identification on the M-CHAT was associated with internalizing behavioral problems on the Child Behavior Checklist (CBCL; Achenbach, 2002) and with socialization and communication deficits on the Vineland Scales. Lower birth weight and gestational age, male gender, chorioamnionitis, acute intrapartum hemorrhage, illness severity on admission, and abnormal MRI also were all significantly associated with receiving an above cutoff score on the M-CHAT. The authors suggest that early markers for ASD might be an under recognized characteristic of very low birth weight infants. Kuban et al. (2009) replicated these finding and reported that in their sample 21% (212/998) of the infants born before 28th week of gestation screened positive for ASD on the M-CHAT. Major motor, cognitive, visual, and hearing impairments were more prevalent in the group which scored positive on the M-CHAT, suggesting that neuro-cognitive impairments might confound the M-CHAT scoring and interpretation. For example, the parent of a child with severe motor impairment may mark as abnormal such items on the M-CHAT screen as “does not point to indicate interest” or “does not bring objects to you”, 2 of the critical items on the M-CHAT, even though the child may demonstrate no language or social impairment. Yet, in children without such impairments, the rate of positive screening was still 16%, nearly 3 times higher than expected in unselected populations. It may also be the case that ASD are actually associated with neuro-cognitive impairments and/or more general neurodevelopmental problems. This suggestion is supported by Hack et al. (2009) who followed up a sample of 219

ELBW children to age 8 years and found increased rates of anxiety disorders and ADHD, as well as elevated rates of ASDs.

Gardner et al. (2008) also report partial data on very early behavior predictors of ASD in NICU infants. In their longitudinal study, approximately 1.5% of the NICU infants were eventually diagnosed with ASD, indicating more than a 2-fold risk of ASD in this sample, with diagnosed ASD children being predominantly male, with higher-educated mothers, and born at lower gestational age and birth weight. They reported that ASD children exhibited a pattern of behavioral deficits starting in the newborn period. Their neonatal neuro-behavior status at 1 month showed higher incidences of visual asymmetry, increased hypertonicity in arms, and better head extension compared to a matched comparison group of NICU babies without an outcome diagnosis of ASD. At 4 months these children had poorer arousal modulation of visual attention which was exhibited by showing greater stimulus seeking. As early as 7 and 10 months, their Bayley-II motor and mental scores were lower than those of the comparison group. The authors suggested that infants who are later diagnosed with ASD might form a distinct sub-population within NICU-assigned babies, characterized with atypical development of visual, motor, and regulatory processes which could be identified from the early neonatal period, and that these differences might be indicative of precursors to ASD at older ages.

Given the abovementioned findings it appears that it may be important for researchers involved in prospective studies of at risk samples to collect data regarding pre-, peri-, and post-natal development – using both parental report and where possible medical records – and to explore possible associations among these data and the developmental trajectories associated with the prodrome/s of ASDs.

### **Genetics as a risk factor in ASD**

The causes of autism are still largely unknown but there are several lines of evidence to support the predominant effect of genetic factors. Many genetic factors are probably involved in the etiology of ASDs and various genetic markers may be involved with various developmental trajectories and prodromes of the many ASDs. Twin studies show concordance rates between monozygotic twins of 70–90%, whereas dizygotic twins show 0-10% concordance (Bailey et al., 1995; Folstein & Rutter, 1977; Hurley, Losh, Parlier, Reznick, & Piven, 2007; Steffenburg et al., 1989). The prevalence of autism in siblings of autistic individuals is ~5% (Rutter, Silberg, O'Connor, & Simonoff, 1999), considerably higher than the population prevalence of 0.37%. In addition, as shown below, a growing body of literature demonstrates that genetic variations in any of several genes can dramatically increase disease risk and thus constitute an etiological factor for ASDs. It is noteworthy that in some of the few high risk sibling studies reporting outcomes through to the age of 3 years recurrence rates appear to be considerably higher, both for ASD outcomes and for other developmental delays. Yet it is likely that biases operate in such studies including enrolling children who already show worrying signs, particularly in studies where siblings are recruited after 6 months of age (e.g. Landa et al., 2007; Zwaigenbaum et al., 2005).

Although the allelic architecture of autism will probably be revealed only from a large amount of empirical data, current studies indicate that a combination of common and rare variants, including *de novo* mutations (spontaneous mutations as opposed to inherited variations), might account for ASD. Until now, most of the genetic variations that were found to be associated with ASD are rare or *de novo* mutations, however, none of these known causes accounts for more than 1–2% of cases. Since ASD is an early onset disease with an impact on reproductive fitness, it is

likely to be influenced by a combination of rare and common alleles, but with many more rare variants than common variants.

The complex inheritance of ASD and the fact that ASD is relatively common has first led to the suggestion that ASD is a polygenic disease, contributed by risk alleles of relatively high frequencies in multiple genes. The Common Disease/Common Variant (CDCV) hypothesis predicts that the genetic risk is contributed by a combination of loci, each locus harboring a single or a very limited number of common predisposing alleles (Reich & Lander, 2001). The high frequency alleles are expected to be relatively old and thus shared across various populations. Genetic association studies are based on the CDCV hypothesis, and they have limited power if multiple rare genetic variants are the primary cause of ASD. A recent published genome-wide association study (Wang et al., 2009) involving 943 ASDs families (4,444 subjects) and another sample of 1,453 unrelated subjects with ASDs and 7,070 control subjects identified an association between ASD and a SNP (rs4307059) located on 5p14.1. The association was replicated in two other cohorts, including 1,390 subjects from 447 families with autism and another independent cohort of 108 ASD cases and 540 matched control subjects. The associated SNP is located in an intergenic region between *CDH10* (cadherin 10) and *CDH9* (cadherin 9). Both *CDH10* and *CDH9* encode type II classical cadherins from the cadherin superfamily, which represent transmembrane proteins that mediate calcium-dependent cell–cell adhesion. These results represent the first consistently replicated associations of common variation with ASD.

The alternative hypothesis is that genetic susceptibility to ASD is conferred by rare deleterious mutations in any of a large number of genes, with substantial allelic heterogeneity between patients. In addition, ASD could result from none inherited -

*de novo* mutations - which could not be detected by standard linkage and association gene mapping approaches. Statistical analysis of ASD family data has recently suggested that a significant proportion of ASD cases may be the result of dominantly acting *de novo* mutations that have a reduced penetrance in females (Zhao et al., 2007). Further support for this idea comes from a growing list of single genetic lesions, each of which seems to be largely sufficient to cause ASD. This includes large cytogenetic abnormalities, copy number variations (CNVs) and single base mutations. The high concordance rate in monozygotic twins and very low concordance in dizygotic twins also fits with contribution of *de novo* mutations.

Chromosomal abnormalities, such as rearrangements, duplications and deletions, have been identified in 6–7% of ASDs (Marshall et al., 2008). The most frequent changes are duplications of 15q11-13 accounting for 1–2% of cases. Other chromosomal abnormalities observed in multiple patients include deletions of 2q37, 7q31, 22q11.2 and 22q13.3 (Freitag, 2007; Vorstman et al., 2006). Recent studies, using high-resolution microarray technologies, suggest that *de novo* CNVs accounts for about 10–20% of ASD cases (Abrahams & Geschwind, 2008; Sebat et al., 2007). CNVs are segments of DNA for which copy-number differences have been revealed by comparison of two or more genomes and are too small to be identified using a microscope (Feuk, Carson, & Scherer, 2006). The proportion of *de novo* CNVs was found to be different between simplex families (7–10%), multiplex families (2–3%) and non-ASD controls (1%) (Marshall et al., 2008; Sebat et al., 2007). Other researchers have found that deletions and duplications of 16p11.2 account for around 1% of autism cases (Weiss et al., 2008). The most recent whole-genome CNV study on a cohort of 859 ASD cases and 1,409 controls reported that several genes involved in neuronal cell-adhesion or ubiquitin degradation are enriched with CNVs in ASD

cases compared to controls. The genes encoding neuronal cell-adhesion molecules are *NRXN1* (Kim et al., 2008), *CNTN4* (Roohi et al., 2009), *NLGN1* and *ASTN2* and the genes involved in the ubiquitin pathways including *UBE3A*, *PARK2*, *RFWD2* and *FBXO40*.

In addition to CNVs that normally affect multiple genes, a small number of cases with ASD are associated with mutations in a single gene. The direct sequencing approach has identified several coding mutations associated with autism including genes encoding neuroligins and their associated proteins that are important in synaptic function (Durand et al., 2007; Jamain et al., 2003; Laumonnier et al., 2004; Szatmari et al., 2007). There are different type of mutations, including frame shift mutations, missense mutations, small deletions and translocations disrupting the following genes: Neuroligin 4 (*NLGN4*) (Jamain et al., 2003; Laumonnier et al., 2004; Yan et al., 2005), *NLGN3*, *NLGN4Y* (Jamain et al., 2003; Yan et al., 2005), Neurexin 1 (*NRXN1*) (Kim et al., 2008; Szatmari et al., 2007; Yan et al., 2008), *SHANK3* (Durand et al., 2007; Moessner et al., 2007), *PTEN* (Butler et al., 2005; Buxbaum et al., 2007; Goffin, Hoefsloot, Bosgoed, Swillen, & Fryns, 2001; Herman et al., 2007; Orrico et al., 2009) and *CNTNAP2* (Arking et al., 2008; Bakkaloglu et al., 2008). Single gene mutations are also the cause of several syndromes in which ASD is observed at higher than expected frequencies, including Rett syndrome caused by mutations in the *MECP2* gene and fragile X syndrome caused by mutation in the *FMR1* gene.

There is also some evidence for contribution of epigenetic modifications (with no change in DNA sequence) to ASD (Hogart, Nagarajan, Patzel, Yasui, & Lasalle, 2007; Jiang et al., 2004), however the manner and extent of epigenetic involvement remains to be defined. Epigenetic modifications including cytosine methylation and post-translational modification of histones provide a mechanism for modulation of

gene expression that can be influenced by exposure to environmental factors and that may show parent of origin effects. Involvement of epigenetic factors in ASD is demonstrated by the central role of epigenetic regulatory mechanisms in the pathogenesis of Rett syndrome and fragile X syndrome, and single gene disorders commonly associated with ASD (Hagerman, Ono, & Hagerman, 2005; Horike, Cai, Miyano, Cheng, & Kohwi-Shigematsu, 2005; Samaco, Hogart, & LaSalle, 2005).

After a period of frustratingly slow progress, there has been a change in terms of our genetic understanding of ASDs in the past few years, in particular the identification of CNVs and what appear to be more and less familial forms of autism. Whilst this field of inquiry holds promise for future studies; there are still challenges to delineate the specific genetics of ASD, particularly at the level of the individual child and family which may in future allow prenatal genetic counseling and informed family planning.

#### **Informing parents about test results and prevention/intervention**

Primary prevention concerns identification and treatment of symptoms that are early risk markers or prodromes for a disease in order to prevent it. The American Academy of Pediatrics (2004) developed a specific brochure "Is Your One-Year-Old Communicating With You?" to assist parents and professionals in identifying the very early symptoms associated with ASD even before age 18 months. This short brochure includes lists of social and communicative behaviors that infants should be displaying by 12 months, between 12 to 24 months and at 24 months as well as a list of behaviors of concern that may be associated with ASD, including items such as "Doesn't return a happy smile back to you; Doesn't seem to notice if you are in the room; Acts as if he is in his own world; Prefers to play alone; Seems to "tune others

out”; Can say the ABCs, numbers, or words to TV jingles but can’t ask for things he wants”.

In addition, the "Autism A. L. A. R. M." (Johnson, 2004) is a helpful flyer regarding ASD which emphasizes important information regarding ASD and the need for, and benefit of, early identification and intervention. Johnson et al. (2007) recommend screening for ASD at 18 and 24 months and at any other point of time that the parents raise a concern, and offer an algorithm for the surveillance and screening of ASD which is extremely helpful for parents and professionals (pages 1196-1197). Still it is uncertain that ASDs will not develop even if the prodrome status (e.g., deficits in language and joint attention) is identified and prevention programs are applied. Furthermore, children who manifest the prodrome status may or may not develop ASD regardless of primary prevention and intervention programs. We are also faced with the question of what should these ‘preventative’ interventions deliver? Whilst there is an increasing evidence-base for behavioral and social communication approaches to early intervention for young children diagnosed with an ASD (Rogers & Vismara, 2008); these may not be applicable to ‘at risk’ children who have not yet developed the full blown disorder. Ongoing studies are testing developmentally informed parenting interventions that draw on the rich literature of supporting interactions that promote parent responsiveness and sensitivity to an infants’ needs and from other intervention programs with at risk populations with diagnoses other than ASD (Bakermans-Kranenburg, van IJzendoorn, & Juffer, 2003). These intervention programs are also informed by our understanding of putative primary and secondary developmental perturbations that lead to the development of ASDs (Dawson, 2008).

With respect to parents of 'high risk' younger siblings who already have a child diagnosed with an ASD and who are coping with many issues associated with having a child with special needs, as these families have additional children they are not only dealing with the child with the diagnosis but also with the concern of whether their newborn child will or will not be on the spectrum. Our data regarding the developmental trajectories of these siblings is still somewhat limited as most siblings' studies have been initiated only in the last 5-10 years. In the longest-established study to date we (Yirmiya, Gamliel, Shaked, & Sigman, 2007) report that some siblings show some delays in language development during the second and third year of life, but that for some SIBS-A, these delays were caught up without any intervention by age 54 month. We also highlight the various developmental trajectories in the preschool years, with some of the young siblings exhibiting continuous difficulties in language, whereas others reveal transient difficulties, and still others revealing difficulties for the first time only after the preschool years, at the ages of 7 and 10 years (Gamliel et al., 2009; Seidman et al., in press). Several explanations were presented for these difficulties including the possibility of a "sleeper effect" trajectory or the possibility of different underlying mechanisms for language development in the preschool years (Rogers, 2009).

These data raise an important question regarding the threshold which ethically and clinically necessitates informing parents. When genetic information is available, there is no doubt that we should inform parents of any information that may be useful to them and their offspring. Yet what should the guideline be regarding informing parents about the development of their younger child and recommending further assessment, and or prevention and or intervention programs? Families who have a child with an ASD are busy families who are most likely already receiving services

for their child with the ASD. Should we refer them out for further services such as prevention and intervention programs for their younger child? What criteria should lead the field in making such recommendations? And if parents are not concerned about the development of their younger child, when should we introduce concerns? These are important issues for researchers and clinicians studying and working with these families (see Zwaigenbaum et al., 2009; for discussion).

## **Conclusions**

The diagnostic criteria for autistic disorder in the DSM-IV-TR (American Psychiatric Association, 2000) and the ICD-10 (World Health Organization, 1992) describe behaviors and impairments in three domains: qualitative impairments in reciprocal social interaction, impairments in communication and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. As can be seen in the current review, the attempt to describe the prodrome involved, and yielded, findings pertaining to antecedents in these three domains. The prodromal behavioral indicators include delays and impairments in early social-communication and social relating behaviors, as well as the earliest emerging signs of rigid and stereotyped behaviors and interests. Many of these indicators have been identified and confirmed in the home video, populations screening and high risk sibling studies reviewed above. However, although we have a list of early markers and risk factors, we still do not have an in-depth understanding or a description of one or more developmental trajectories for the prodrome of ASDs and for the various different ASDs. Some ASDs are recognizable earlier (i.e., 'core' Autistic Disorder (DSM-IV) or Childhood Autism (ICD-10)), especially when accompanied by a delay in language milestones and

intellectual disability) and others later on (i.e., Asperger's Syndrome with normal or even advanced language development and intelligence).

Furthermore, some cases of ASDs involve genetic (some familial; some sporadic) and environmental contributions (e.g. peri-natal) whereas others may not, and the transaction among genetics and environment may vary tremendously even among individuals with the same ASD diagnosis. Although it is clear that these causative factors affect brain development, organisation and function in a way that leads to the ASD phenotype; we have not yet identified prodromal brain markers that securely signpost the later emergence of full blown disorder and the extent to which any of these markers will be specific to autism, as opposed to a range of other neurodevelopmental outcomes is not known. Similarly, behavioral phenomena such as regression, epilepsy and developmental delays, amongst others, also vary among individuals with ASDs. Taken together, these many variations may make the search for a unifying prodrome extremely difficult or even impossible. The heterogeneity of causation and manifestation of ASDs makes the search a unifying prodrome perhaps a lost cause both for science and for clinical practice.

As we combine our efforts and study cohorts of children at risk for ASDs taking into account genetic and environmental factors, as well as specific behavioral profiles of the children, we hope to find out more about the aetiology of ASDs. In future this may allow us to develop a different, more elaborated and more empirically-based nosological systems than those currently employed in the diagnostic manuals and be able to better delineate the prodromes of the various ASDs. This holds out the promise of improving

efforts at early identification and the possibility to develop and test interventions that may lessen the neurodevelopmental perturbations that lead to the ASD phenotype; shifting the trajectory of individuals and improving outcomes for children and their families. Whilst progress in science and clinical practice can be frustratingly slow; our understanding of the early emerging ASD phenotype has undergone a revolution in the past 20 years. The challenge for the next decade is to improve our understanding of the underlying biological and environmental influences that lead to the ASD phenotype; and to identify prodromal signs that will help mark out infants at risk before the onset of the disorder.

- Several novel lines of investigation have been employed, including retrospective coding of home videos, prospective population screening and ‘high risk’ sibling studies.
- Other methods include investigation of pre- and peri-natal, brain developmental and other biological factors.
- Whilst no single prodromal sign is expected to be present in all cases, a picture is emerging of indicative prodromal signs in infancy.
- The most common early behavioral signs noticeable towards the end of the first year of include social communication abnormalities but also possibly regression, attention, and motor signs.
- There is great interest in several apparent atypicalities in brain structure, connectivity and function, although it remains to be determined how specific these will be to ASD.

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Table 1

*Home video studies*

Reference	<i>N</i>	Age (Months)	Comparison group	Findings
Losche (1990)	8	4-12m, 13-21m, 22-30m, 31-42m	TD	Less goal directed action from 4-12m; impairment in sensorimotor development from 13-21m; reduced role as 'social actor' from 22-30m
Adrien et al. (1991, 1993)	12	0-12m, 13-24m	TD	Before 12m: social attention, communication, motor behaviors; 13-24m: as above plus gaze avoidance, hypoactivity, absence of emotional expression
Osterling & Dawson (1994)	11	12m	TD	Less pointing, showing, looking at others and responding to name
Werner et al. (2000)	15	8-10m	TD	Less orienting to name, marginally less looking at others faces while smiling
Osterling et al. (2002)	20	12m	ID, TD	Less orienting to name, less looking at people
Werner & Dawson (2005)	36	12m; 24m	ASD with and without regression; TD	At 12m infants with ASD with no regression ('early onset autism') showed fewer joint attention and communication behaviors than infants with ASD with later regression and TD infants; At 24m both ASD groups had fewer words, vocalizations, declarative points, social gaze and orienting to name, than TD group
Mars et al. (1998)	25	12-30m	TD	Autism < PDD/TD for social interaction and communication (e.g. joint attention)
Baranek (1999)	11	9-12m	ID, TD	Reduced response to name and orientation to visual stimuli compared to ID group

Table 1 (continued)

*Home video studies*

Reference	<i>N</i>	Age (Months)	Comparison group	Findings
Maestro et al. (2001, 2002, 2005)	15	0-24m	TD	Abnormalities in intersubjective behaviors (anticipation of another's aim and imitation) and poor attention to social but not non-social stimuli (objects) in first 6m; impaired

Autism prodrome 83 of 89

				symbolic play between 6-24m
Phagava et al. (2008); Esposito et al. (2009)	18	0-5m	TD	Abnormal fidgety movements and lower levels of movement/motor symmetry in autism group
Clifford et al. (2007)	15	12-24m	ID/LD, TD	Reduced eye contact, response to name and anticipatory gestures compared to ID/LD group
Clifford & Dissanayake (2008)	22	0-24m	TD	Impairments in gaze and affect in first 6m; impairments in joint attention behaviors during second year
Ozonoff et al. (2008)	54	0-24m	ASD with and without regression; ID, TD	Autism and ID show delay in motor milestones compared to TD; Motor abnormalities when sitting and prone and lack of protective response seen in ID but not autism group

ID = Children with an intellectual disability; LD = Language delay; TD = Typically developing children

Table 2

*Prospective screening studies*

Reference		Age (Months)	Study design	Administration	Key items/content	Instrument parameters
Baron-Cohen et al. (1992, 1996); Baird et al. (2000)	CHAT	18m	High risk sibling design; 2-stage population screening ( $n = 16,235$ )	Parental questionnaire and health practitioner observation	Joint attention; pretend play	Sensitivity = 38% (1-stage) Positive predictive value = 26% (1-stage); Positive predictive value = 83% (2-stage)
Willemsen-Swinkels et al. (2006); Dietz et al. (2006)	ESAT	14m	2-stage population screening ( $n = 31,724$ )	Health practitioner completes items following interview with parents	Initial screen: play, emotional expressions, sensory oddities; Follow-up screen: above plus early social communication behaviors	Positive predictive value for ASD = 25% (2-stage); Positive predictive value for all neurodevelopmental disorders = 68% (2-stage)

Table 2 (continued)

*Prospective screening studies*

Reference		Age (Months)	Study design	Administration	Key items/content	Instrument parameters
Robins et al. (2001); Kleinman et al. (2008)	M-CHAT	24m	Combined high-risk: early intervention referrals ( $n = 484$ ) and population screening ( $n = 3,309$ )	Parent questionnaire	Most discriminating items: joint attention behaviors and social relatedness	Positive predictive value = 36% (1-stage); Positive predictive value = 74% (2-stage)
Wetherby et al. (2004, 2008)	ICT	9-24m	Population screening ( $n = 5,385$ ); multiple stage follow-ups	Parent questionnaire	Early social communication behaviors; emotional response	Positive and negative predictive value at or higher than 70% for all age groups except 6 to 8m
Reznik et al. (2007); Watson et al. (2007)	FYI	12m	Pilot population study ( $n = 1,496$ )	Parent questionnaire	Full range of possible early autism abnormal signs	Follow-up studies not yet conducted

CHAT (Checklist for Autism in Toddlers); ESAT (Early Screening of Autistic Traits); M-CHAT (Modified- Checklist for Autism in Toddlers); ICT (Infant Toddler Checklist); FYI (First Year Inventory)

Table 3

*High risk sibling studies*

Reference	N (SIBS-A)	Age (Months)	Comparison group	Findings
Zwaigenbaum et al. (2005)	65	6-24m	TD $n = 23$	Temperament characteristics (decreased activity) at 6m and behavioral markers (e.g., orienting to name, social smiling) and language delays at 12m - predicted later ASD at 24m Siblings with ASD at 24m had more delays in gestural communication (i.e., giving, pointing, and nodding head) at 12m Siblings with ASD at 36m showed early impaired social-communicative development (e.g., lack of interest in others), behavioral markers (e.g., visual fixation, repetitive behaviors), distinct temperament profile (e.g., intolerance of intrusions, dysregulated state) – associated with the emergence of autism. Signs of autism emerged earlier (12m) in siblings with a decrease in IQ "Hands to ears" posture at 18m was more frequent in the high risk group compared to the controls. Siblings with a later ASD diagnoses "arm waved" more frequently at 12m and 18m. The ASD and control groups had considerable overlap in their repertoires of stereotyped behaviors
Mitchell et al. (2006)	97	12-24m	TD $n = 49$	
Bryson et al. (2007)	9	6-36m		
Loh et al. (2007)	17	6-36m	TD $n = 15$	

Table 3 (continued)

*High risk sibling studies*

Reference	N (SIBS-A)	Age (Months)	Comparison group	Findings
Landa & Garrett-Mayer (2006)	60	6-24m	TD $n=27$	At 6m no significant differences emerged among the three groups (ASD, LD, unaffected diagnosed at 24m) on the MSEL. At 14m the ASD group performed significantly poorer than the unaffected group on most of the MSEL scales. By 24m the ASD group performed significantly poorer than the unaffected group on all the MSEL scales and significantly poorer than the LD group on the Gross and Fine Motor and Receptive Language scales. ASD group had the slowest developmental trajectory, with a significant decrease in development between 14m and 24m
Landa et al. (2007)	98	14-36m	TD $n=17$	The ASD early diagnosis subgroup differed at ages of 14m and 24m from all other groups (ASD with late diagnosis, BAP, and non-BAP) in their communication and play behavior.
Nadig et al. (2007)	46	6-24m	TD $n=25$	At 6m no significant differences emerged between siblings and controls in orienting to name. However, at 12m all controls oriented to calling their name compared to 86% of the siblings. 75% of the siblings who failed to respond to their name being called were identified at age 24m with ASD or with other developmental delays.

Table 3 (continued)

*High risk sibling studies*

Reference	N (SIBS-A)	Age (Months)	Comparison group	Findings
Merin et al. (2007)	31	6m	TD <i>n</i> =24	10 of the 11 infants with diminished gaze to the mother's eyes relative to her mouth during the Still Face were SIBS-A. No significant differences emerged between the two groups in affective displays (i.e., smiling, negative affect), in the total amount of fixation time, or in the fixation directed at the face versus other areas
Young et al. (2009)	33	6-24m	TD <i>n</i> =25	All three siblings with ASD at 24m (2 SIBS-A, 1 SIBS-TD) demonstrated consistent eye contact and typical affective responses at 6m during the Still face. No associations were found between face scanning and affective responses at 6m and the continuous measures of autism symptom frequency or symptom severity at 24m. Diminished gaze to the mother's eyes relative to her mouth at 6m predicted higher scores of expressive language at 24m
Ozonoff et al. (2008)	35	12-36m	TD <i>n</i> =31	Siblings with later ASD had increased frequency of spinning, rolling and rotating the objects and prolonged visual inspection at 12m. Repetitive behaviors at 12m were significantly related to cognitive and symptomatic status at the 36m outcome

Table 3 (continued)

*High risk sibling studies*

Reference	N (SIBS-A)	Age (Months)	Comparison group	Findings
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Autism prodrome 89 of 89

Yoder et al. (2009)	43	15-34m	TD $n = 24$	Weighted triadic communication (i.e., use of gestural, vocal, gaze, and/or symbolic communication that shows attention to the message recipient and the physical referent of communication), responding to joint attention, and initial language age equivalence were associated with later ASD diagnosis
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LD = Language delay; TD = Typically developing children; MSEL = Mullen Scales of Early Learning (Mullen, 1995); SIBS-A = Siblings of children with autism; SIBS-TD = siblings of children with typical development; m = months