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The Origins of Social Impairments in Autism Spectrum Disorder: Studies of Infants at Risk

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Abstract

Core impairments in social and communicative behaviors are among the defining characteristics of autism spectrum disorder (ASD), making this a model syndrome for investigating the mechanisms that underlie social cognition and behavior. Current research is exploring the origins of social impairments in prospective longitudinal studies of infants who are at high risk for ASD, defined as having an older sibling with the disorder. Behavioral studies that have followed these infants through to outcomes have found that during the early months of life they are no different from typically developing infants; they are socially interested, engaged and enjoy interactions with people. By the end of the first year risk signs for later ASD can be identified though no single marker has been identified. It seems that an aggregate of risk markers together may be need to predict ASD. Other studies have compared infants at risk for ASD to low risk controls to identify neurocognitive endophenotypes. Several differences in subtle aspects of behavior and in brain organization have been found in infants younger than 12 months, though it is not known whether these differences are also risk markers for a later ASD diagnosis. The findings from these line of research are used to provide a new view of ASD, as a disorder defined on the basis of alterations in the developmental trajectories across multiple domains. ASD is an emergent disorder that is characterized by the loss of social communication skills in the period between 9 and 24 months. Across children the rate, timing and severity of this loss is highly variable. Future research will lead to a greater understanding of the genetic and neurocognitive mechanisms that underlie these fundamental changes in the developmental patterns of individuals with ASD.

Introduction

Autism spectrum disorder (ASD) is an umbrella term for a set of neurodevelopmental disorders (autistic disorder, pervasive developmental disorder-not otherwise specified, Asperger syndrome) that are defined primarily by core impairments in social-communication (APA, 2000). ASD is diagnosed on the basis of behavioral symptoms that include: unusual eye-contact, limitations in facial expressions directed to other people, atypical social engagement and responsiveness, difficulty with peer relationships, lack of awareness or understanding of other people's thoughts and feelings, poor communication skills, difficulty initiating social contacts through verbal or non-verbal means, rigid or unusual behaviors and restricted interests. ASD is typically identified during the preschool period, though nowadays can be discerned by

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experts by age two (Chawarska, Klin & Volkmar, 2008). The symptoms are readily observable during face-to-face interactions with children and adults with ASD, and, although there is considerable variability in these primary symptoms as well as in associated atypical behavioral patterns (including intellectual disability, language impairment, unusual responses to sensory stimuli and challenging behaviors), core deficits in *social functioning* define and distinguish ASD from other developmental disorders. For this reason, ASD is model syndrome through which we can investigate social perception, cognition and behavior.

By the age of three, children with ASD show striking deficits in all aspects of social behavior. But when do these impairments begin? What are the developmental precursors or origins of atypical behavior in ASD? Typically developing infants are remarkably social creatures. For example, at birth they show preferences for social stimuli and recognize their mothers on the basis of some distinctive features; they prefer direct eye-gaze; and they smile at other people by 2 months of age (Johnson, Grossman, & Farroni, 2010). Are differences in infants who will eventually be diagnosed with ASD evident from birth? How do these infants change during the first year of life? Can we identify any specific behaviors that may be the earliest manifestation of ASD before the onset of the full-blown syndrome? Although there is so much heterogeneity among children and adults with ASD, at the earliest developmental stages is there more uniformity in both atypical behaviors and developmental patterns before the onset of the full-blown syndrome? We explore these questions in this paper, with the goal of evaluating what might be learned about some of the fundamental mechanisms that underlie the emergence and development of social engagement in young children.

Early Development in Autism

Autism was first ‘discovered’ by Leo Kanner (1943). He believed that autism was present at birth and manifest in the earliest months of life, citing as examples of behavioral disturbance the lack of anticipatory posture (raising arms) shown by infants when being picked up by their mother, and the preference for infants later diagnosed with autism to be alone. Other behaviors noted by some parents include lack of social interest or smiling and lack of social responsiveness, which, together, suggest that autism may indeed be present at birth (Zwaigenbaum et al., 2007). The problem with these examples is that they come from retrospective recall, which is notoriously plagued by bias: once you know your child has autism, you may selectively remember those times when as a baby he was content to stay in his crib and not seek comfort while forgetting all the occasions when he was socially engaged. During the 1990s several studies were published that relied on more objective evidence about the early behavior of infants who were later diagnosed with ASD: observations of home video recordings (e.g., Adriene et al., 1993; Osterling & Dawson, 1994). These studies found that at 12 months of age there were quantitative differences in the infants’ behavior, including reduced eye contact, lack of response to their own name, and limited social engagement (e.g., Baranek, 1999). But most of these studies, too, have methodological weaknesses such as the absence of good control data, bias in the selection of infants and in the recordings offered to researchers (Zwaigenbaum et al., 2007). Moreover, there are no studies that have analyzed videos going back to the earliest months of life, and the lack of experimental control means that video-recordings can only be used to observe the infants’ overt behaviors without access to information about how they perceive or attend to social stimuli.

Prospective Studies of Infants at Risk

More recently, a new methodological approach for investigating the early development of infants later diagnosed with ASD has been introduced: prospective longitudinal studies of infants ‘at risk’ for ASD (Elsabbagh & Johnson, 2007; Rogers, 2009; Zwaigenbaum et al., 2007). In most of the these studies risk is defined in terms of *genetic* risk. Based on twin and

family research it is well known that ASD is a highly heritable complex genetic disorder (see Abrahams & Geschwind, 2008 for a review). Thus, siblings of children diagnosed with ASD are significantly more likely to meet criteria for this disorder than children in the general population. Current estimates vary, but are now considered to be between 15% and 20% among infants at genetic risk, compared to less than 1% among low-risk infants (Rogers, 2009). Research designed to identify the earliest risk signs for ASD builds on these findings by studying infant siblings of older children with a confirmed diagnosis of ASD (referred to as high risk infants) and comparing them to infants at low risk for ASD, usually defined as infants with an older typically developing sibling, to control for birth order effects, who are recruited from families with no history of ASD. Because infants in these studies are typically followed from the first year of life, some even from birth, so-called 'infant sibling' studies are able to shed light on the early development of social-communicative behaviors, as well other related behaviors, to identify when differences can be identified in infants who later receive a diagnosis of ASD (Zwaigenbaum et al., 2007).

Even siblings who do not develop ASD are more likely to share some of the characteristic features, usually at a less severe level, of the ASD phenotype. This is often referred to as the 'broader autism phenotype' (e.g., Piven et al., 1997). Studies of older children have found that siblings and other first degree relatives (parents), are more likely to show mild impairments in language (Lindgren et al., 2009), non-verbal communication (Ruser et al., 2007), theory of mind (Baron-Cohen & Hammer, 1997) and face processing (Dawson et al., 2005) compared to controls. Relatives also share with individuals with ASD some of the atypical patterns of brain structure and function which underlie social-communicative behaviors (Dalton et al., 2007; Dawson et al., 2005; Lindgren et al., submitted), suggesting that these neurocognitive features may serve as phenotypic markers of risk associated with ASD - or endophenotypes (Gottesman & Gould, 2003). Research on infants at risk for ASD therefore may not only identify precursors to a later ASD diagnosis, but can also provide important clues to the origins of endophenotypes for ASD and ultimately will clarify why some infants at risk with these features do not develop the disorder while others do.

Infants at Risk in the First Year of Life: Behavioral Markers of Risk

Several behavioral studies have been published on infants at risk who are 6 months or younger, using primarily standardized measures of cognitive and language development, and specially developed structured assessments of atypical behavior in infants that might be early indicators of autism symptoms (Bryson et al., 2006). The consensus from these investigations is that during the earliest months of life there are no clear differences between infants who later meet criteria for ASD, other high risk infants, or low risk controls. These babies all show clear social interest and engagement, they smile at other people, especially their primary caregivers, they follow eye gaze, vocalize and have good eye contact during face-to-face interactions (see Rogers, 2009). In one recent study, which followed a relatively large cohort of infants at risk, the infants with an ASD outcome at age 3 showed *more* frequent social and communication behaviors at 6 months than the low risk infants who had a normal outcome (Ozonoff et al., 2010). Thus, prospective studies provide no evidence for very early deficits in social engagement during the infancy period.

By 12 months, however, there are significant differences in the infants who go on to develop ASD, hinting at a fundamental change in social communication as well as other behaviors taking place between 6 and 12 months. What are some of the behaviors that have been identified at 12 months? A small number of children begin to show slight delays in fine or gross motor development at this age, though for most children this is a pattern that emerges later during the second year of life (Landa & Garrett-Mayer, 2006). Within the motor domain, some children show unusual repetitive behaviors that involve atypical arm waving movements (Iverson &

Wozniak, 2007; Loh et al., 2007). Differences in visual attention are also risk signs for ASD. One example is atypical looking at objects, such as looking at objects from the corner of one's eyes or staring for an unusually long time at simple objects (Ozonoff et al., 2008). Other attentional problems include difficulty disengaging attention from one visual stimulus and shifting attention toward a novel stimulus (Zwaigenbaum et al., 2005). In addition to these motor and visual behaviors, more direct signs of social-communication impairment are also found at 12 months. These infants show reduced eye contact, social smiling, social interest, imitation, reduced responding to bids for joint attention, as well as reduced responding to their own name (Nadig et al., 2007; Ozonoff et al., 2010; Presmanes et al., 2007; Zwaigenbaum et al., 2005). It appears that these differences in joint attention and response to name reflect social interest and motivation (and not more basic visual or attention deficits) in that they correlate most closely with other behaviors related to initiating social engagement with other people (Rogers, 2009). Finally, even at 12 months delays are already evident in both nonverbal gestural communication and in language. Infants who later develop ASD are less likely to intentionally communicate with others using either pointing or other social gestures (Mitchell et al., 2006).

Importantly, no single atypical behavior has been found that is shared by all 12 month olds who later go on to meet criteria for ASD. Instead, as with the diagnosis of ASD itself, there is a constellation of social, attentional and motor behaviors that may be considered risk markers (Zwaigenbaum et al., 2005). If a baby exhibits several of these behaviors at 12 months, specifically, 7 or more risk markers, they are more likely to meet diagnostic criteria for ASD at a later age (Zwaigenbaum et al., 2005). In this way studies of infants at risk reflect the *complex* nature of the disorder. ASD is complex (heterogeneous) in terms of its genetic basis, range of behaviors and severity of phenotypic expression, and now has been shown to be complex with respect to the range of phenotypic risk markers. Current genetic studies suggest that the majority of ASD cases may be explained by a large number of variable genetic risk factors, each variant conferring small risk. On this model, ASD likely requires multiple risk genes that interact with each other and the environment (Abrahams & Geschwind, 2008). There is also growing evidence that between 10% and 20% of ASD cases may be explained by unusual chromosomal rearrangements, mutations in specific ASD genes, or copy number variants (deletions or duplications), often arising *de novo* and presenting as more severe cases accompanied by intellectual disability. Among infants at risk, occasionally a young infant (below the age of 12 months) already shows atypical behaviors, usually sensory or motor patterns, although as noted, this is not found in the majority of infants (cf. Bryson et al., 2007). These infants invariably go on to have more severe ASD symptoms as well as intellectual disability. One possibility is that these infants who show very early signs may also have unusual copy number variants or other submicroscopic chromosomal anomalies, which would be consistent with their phenotype.

To summarize: the vast majority of infants at risk who later go on to have ASD show no signs at 6 months; at 12 months although there is no single atypical behavior that signals risk for ASD, there is a set of social communicative, motor and attention behaviors that together can predict later diagnosis. A few rare cases of infants do show unusual behaviors before the first birthday. One possibility is that these cases are marked by atypical genetic risk factors too, in the form of chromosomal anomalies. The findings suggest, then, that the pathway to atypical social-communicative impairment defining of ASD begins to emerge during the latter half of the first year of life, and varies considerably among infants.

Infants at Risk in the First Year of Life: Endophenotypes in Siblings

As noted earlier, first degree relatives exhibit a number of behavioral and neurobiological characteristics that are evident in ASD, particularly in the domain of social cognition and communication. Several studies of infants at risk have explored the emergence of

endophenotypes using more sensitive cognitive or electrophysiological measures using cross-sectional experimental designs. In most of these studies groups of high risk infants are compared to low risk infants, without regard to later outcomes. The findings from these studies should be viewed with caution because it may be that in some cases significant group differences are driven by outliers who later would receive an ASD diagnosis. Nevertheless, this line of research offers a provocative view of the very early development of infants who carry genetic risk for ASD.

Elsabbagh and colleagues (Elsabbagh et al., 2009a) followed up on earlier studies showing atypical attention at 12 months using reaction times in looking behavior during an experimental task. They compared high and low risk infants at 9-10 months of age on an attention disengagement paradigm. The high risk infants took longer to disengage from a central stimulus and, unlike the low risk infants, did not find it easier to disengage when a 200 millisecond gap was inserted between the initial central stimulus and the peripheral distracter. Another study investigated working memory for social and non-social stimuli in infants at 6 and 9 months of age (Noland et al., 2010). The main findings were that performance on the social stimuli was the same in the high and low risk groups, however, the high risk group performed significantly better on the non-social stimuli. These findings are especially interesting as they suggest that the endophenotype may have more to do with differences in the processing of objects rather than people. Moreover, studies of atypical attention (Elsabbagh et al., 2009a; Ozonoff et al., 2008; Zwaigenbaum et al., 2005) generally use non-social stimuli so stickier attention or unusual looking behaviors may be the result of enhanced interest in objects, which could later be reflected in superior perceptual and attention performance in older children and adults with ASD (Mottron, Dawson, & Soulieres, 2009).

Electrophysiological (EEG) studies have investigated neural responses to faces in 10 month old infants. Elsabbagh and colleagues (Elsabbagh et al., 2009b) measured event-related potentials (ERP) to female faces with direct or averted gaze. The early components of the face responsive ERP (PI and N290) were the same in the high and low risk infants. In contrast, the P400, a later component that is sensitive to top down visual processes perhaps related to computing the communicative or affective significance of eye gaze, had a significant longer latency for direct gaze among the high risk infants. These infants also show increased oscillatory activity in the gamma band at baseline and during the task over central and temporal brain regions using time frequency analysis, which is taken as a possible marker of atypical neural connectivity. The findings suggest that although the neural mechanisms underlying face processing are not impaired in infants at risk, they do show differences related to neural processing of eye gaze direction, and their brains may also have altered connectivity, as has been found in older children with ASD using EEG (Murias, Webb, Greenson & Dawson, 2007) and other methods (see Belmonte et al., 2004). Another ERP study also explored face processing in 10 month old infants at risk (McCleery et al., 2009). In this study McCleery and his colleagues analyzed infants' N290 and P400 responses to familiar and unfamiliar faces and objects. Their main findings were that the high risk infants showed faster N290 and P400 responses to objects, but there were no group differences in latency of responses to faces. Instead, they found that the high risk infants showed reduced hemispheric asymmetry in ERP responses, suggesting that lateralization of brain organization for face processing may fail to develop during the first year of life in infants at risk. In a recent study of speech processing in infants at risk, a similar pattern of failure to develop functional lateralization for language in 9 and 12 month-olds was also found (Seery et al., 2010). It is interesting to note that differences in brain organization and connectivity in high risk infants emerge in the same period when accelerated head growth has been found in children with autism (Redcay & Courchesne, 2005).

Behavioral studies have also compared high and low risk groups of infants and while most have not found differences, a few findings have been reported in the literature (Rogers,

2009). Nadig et al. (2007) found that compared to low risk infants high risk infants showed less preference for infant-directed speech relative to adult-directed speech, though there was wide variability in preferences found in both groups. The still-face paradigm, which involves dyadic interaction between babies and their mothers who alternate between engaged interaction and neutral disengaged segments, has been used in several studies with 4-6 month old infants. Yirmiya and her colleagues (Yirmiya et al., 2006) reported that at 4 months, high risk infants (none of whom later received an ASD diagnosis) were slightly less synchronous in their interactions with their mothers and more likely to show neutral affect. Cassel et al. (2007) reported less smiling during the face-to-face interaction in high risk 6 month olds. And Merin et al. (2007) found that 6 month old high risk infants were more likely than low risk infants to look more at their mothers' mouth than her eyes during the interaction phases. Interestingly, Young et al. (2009) followed up the high risk infants in this latter study through to outcome and found that not one of the high risk infants who preferred to look at the mouth was later diagnosed with ASD. Instead, preference for looking at the mouth at 6 months predicted higher expressive language scores at age 2. These findings suggest that there may be subtle differences in the social-affective behavior of infants at risk for ASD but that these behaviors are not predictive of later outcomes.

Taken together, the studies of infants at risk demonstrate that subtle behavioral and neurobiological endophenotypes may be identified in the first year of life *before* the onset of risk signs at around 12 months that are associated with a later diagnosis of ASD. But there is still a great deal that we do not know about early development and risk for ASD. First, many of these studies have not followed the infants through to outcome so what is reported here as patterns associated with the broader autism phenotype at a group level may in fact be risk signs for ASD, exhibited by outliers in the high risk group. Second, how specific are the findings summarized here to ASD? Since none of the reported studies include a comparison group of infants at risk for other disorders (e.g., attention deficit disorder, specific language impairment, dyslexia, anxiety) we do not know whether any or all of the group differences would also be found in different populations. Third, are these endophenotypes inter-related? For example, do the same infants who show reduced lateralization for faces also show reduced lateralization for language? Do infants who show faster ERPs to objects also show differences in visual disengagement? Is a slower P400 to direct gaze associated with preference for looking at the mouth? Answers to these kinds of questions, which will require larger samples of infants, will help us to understand the neurocognitive mechanisms that underlie these endophenotypes. A related and final question addresses the distinction between an endophenotype (found in siblings but not related to diagnosis) and a risk marker (which is associated with later ASD): is this distinction real or just apparent, based on differences (whether risk groups are compared, or infants followed until a diagnosis can be made) in the design of studies that have been published thus far? If there is no fundamental difference between an infant-level endophenotype and a risk marker then it may well be that ultimately risk for ASD might be based on a cumulative model: the more endophenotypes present in an individual infant, the more likely that infant is to go on to meet criteria for ASD (cf. Zwaigenbaum et al., 2005).

Defining Autism Spectrum Disorder

Infant studies have revealed that social communicative impairments are not present during the first few months of life. The period between 6 and 12 months seems to be critical; it is a time when many neurobehavioral differences begin to emerge in high risk infants, but for the most part these differences are subtle, quantitative, and highly variable among this group of infants. No single behavior, or even developmental domain, is predictive of outcome. Rather, ASD appears to emerge gradually over time. The rate of emergence varies significantly but the defining feature of ASD seems to alterations in the expected developmental trajectories across multiple domains. For some domains there may be a plateau or slowed developmental rate

(e.g., motor, cognitive and in some cases, language). In other domains, specifically in social communication, which is at the core of ASD, the altered developmental trajectory may be defined as loss of previously acquired skills.

It used to be thought that regression, defined as a period of normal development followed by a significant change in which there is a loss of previously acquired language and other skills, was a pattern associated with about a quarter of the ASD population (Luyster et al., 2005). Studies of infants at risk suggest that regression, defined specifically in terms of a gradual loss of social communication skills, may be characteristic of *all* children with ASD (Ozonoff et al., 2010). There is some evidence to suggest that this definition of ASD may distinguish this complex neurodevelopmental disorder from others with which it is closely associated, including specific language impairment (Pickles et al., 2009). On this view, infants who once were interested in people, looked at their eyes and faces, followed eye gaze, and initiated and responded to social interactions, gradually lose these skills in the period between around 9 and 24 months. The onset, timing, and severity of the loss varies widely across children (Ozonoff et al., 2010) and it is likely that some children who experience these losses and meet criteria for an ASD diagnosis during the preschool years, later regain the skills and appear to have 'recovered' - almost always in the context of intensive behavioral interventions (Sutera et al., 2007).

Studies of infants at risk have provided us with a fundamentally new view of ASD, and in particular the onset of the social and communicative impairments. But there is still a great deal that we do not know. Gradual loss of connection with the social world begins in the latter half of the first year of life. This is a period of significant cognitive change that is seen across development. Within the social domain perceptual expertise for speech and faces emerges as a result of experience-dependent learning; infants form attachments to their primary caregiver and become wary of strangers; joint attention and intentional communication skills emerge. The infant, who is now mobile and independent, becomes more actively engaged with the environment and learning from the surrounding culture (see Meltzoff et al., 2009). These advances all take place in the context of a rapidly changing brain (Kagan, 2008). But what precipitates the different developmental path taken by infants with ASD? What critical neural mechanisms underlie the differences? Is ASD driven by the *loss* of motivation to engage in the social world, or is it more related to greater engagement in the world of objects? Whatever the answers may turn out to be, prospective studies of social cognition and social behavior in infants at risk for ASD will provide important clues to the mechanisms that drive developmental changes in this domain in all infants.

We still have a great deal to learn about the early development of infants who later are diagnosed with ASD, though given the current pace of research on high risk infants we can expect to continue making significant progress unraveling the complexity of this disorder in the coming years. It is likely that there is no one pathway to ASD though ultimately it may be that when we can include genetic risk factors, many of which are likely to be associated with learning and the timing of brain development, some of the variability in the developmental trajectories will be explained. We may never find the single clue (genetic, neurobiological, behavioral) that can unequivocally predict who will have ASD --it simply may not exist. Instead, ASD may be more accurately viewed as an emerging syndrome that unfolds over time in a probabilistic way as a result of alterations in the dynamic interaction between the infant and his or her environment. The clues to predicting this emergence need to be pieced together across different levels of risk markers including genetic, demographic, neurobiological and behavioral, each of which provides significant information about the individual child and which collectively, may yield a comprehensive profile of the origins of ASD.

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