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CHAPTER 2

Development of Social Brain Circuitry in Autism

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The past two decades have witnessed a tremendous expansion in our knowledge of the neural basis of social behavior. Improved neuroimaging techniques have allowed us to study the brain in action in young children, offering insights into the brain basis of early social behavior. This knowledge has provided new understanding of brain-based disorders that affect social development. In turn, studies of such disorders have provided unique perspectives on the normal development of the social brain.

Autism, most fundamentally, is a disorder of social communication. Young children with autism fail to show early preferences for the social environment; higher-order social behaviors, such as shared attention and theory of mind, are core impairments found in the disorder. As we learn more about the neural basis of autism, we come to understand the biological underpinnings of fundamental aspects of social behavior. Which neural substrates are critical to an ability to imitate others, to share emotional states, and to engage in coordinated, reciprocal interactions with others? When do such neural substrates come on line and how do they influence the child's ability to engage with the social environment, thereby providing the basis and mechanism for further development? These are the types of questions that the disorder of autism poses.

In this chapter, we begin by describing some of the early impairments in social behavior found in autism. Next, a developmental model for the normal emergence of social brain circuitry during early infancy is described, along with a theory of how this development might be disrupted in autism. Finally, we discuss research on the genetic basis of aspects of social behavior and the potential role of this research in understanding the etiology of autism.

EARLY SOCIAL IMPAIRMENTS IN AUTISM

Five domains of social behavior that typically emerge during the first year of life have been found to be affected in autism. As reviewed below, these domains are social orienting, joint attention, attention to others' emotions, motor imitation, and face processing.

Social Orienting

Dawson and her coworkers coined the term "social orienting impairment" to refer to the failure of young children with autism to spontaneously orient to naturally occurring social stimuli in their environment (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998). Mundy and Neal (2001) proposed that the developmental pathway of young children with autism is altered by this social orienting impairment because the children are deprived of appropriate social stimulation. Very early in life, typical infants show remarkable sensitivity to social stimuli (Rochat, 1999). Neonates are naturally attracted to people, including human sounds, human movements, and features of the human face (Maurer & Salapatek, 1976; Morton & Johnson, 1991). For example, infants as young as 5 months observe even very small deviations in eye gaze during social interactions with adults and stop smiling and look away when the adult partner's eyes are averted (Symons, Hains, & Muir, 1998). This early emerging sensitivity and attention to the social world is reflexive rather than voluntary. Very likely, the acquisition of subsequent social behaviors depends on this very early propensity to devote particular attention to people (Rochat & Striano, 1999). Active volitional orienting to a social stimulus, such as head turning when one's name is called, typically emerges by 5–7 months of age. Around this age early joint attention skills also may begin to develop: Typically developing infants between the ages of 6 and 12 months have been shown to match the direction of mother's head turn toward a target (Brooks & Meltzoff, 2002; Morales, Mundy, & Rojas, 1998).

One of the earliest and most basic social impairments in autism is a failure to orient to social stimuli, and this failure almost certainly contributes to the later social and communicative impairments observed in the disorder (Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Mundy & Neal, 2001). Retrospective studies of home videotapes of first birthdays have shown that, in comparison to typically developing 12-month-olds, 1-year-old infants later diagnosed with autism fail to orient to their names, attend less to people, and show impairments in joint attention (Osterling & Dawson, 1994; Osterling, Dawson, & Munson, 2002). A home videotape study examining behaviors in even younger infants demonstrated that 8- to 10-month-old infants later diagnosed with autism were much less likely to orient when their names were called, compared to typically developing infants of the same age (Werner, Dawson, Osterling, & Dinno, 2000). These behaviors are also seen in toddlers with autism. Swettenham and colleagues observed attentional patterns in 20-month-old toddlers with autism, typical development, and developmental delay and found that the toddlers with autism spent less time overall looking at people, looked more briefly at people, and looked longer at objects (Swettenham et al., 1998). Dawson and colleagues demonstrated in two experimental studies that, compared to children with mental retardation without autism and typically developing children, children with autism more frequently failed to orient to both social and nonsocial stimuli, but this failure was much more extreme for social stimuli (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Dawson, Toth, et al., 2004). These studies also indicated that children with autism were more impaired in their joint attention ability; furthermore, severity of their joint attention ability was strongly correlated with social orienting ability but not with nonsocial orienting ability.

Joint Attention

Joint attention is the ability to coordinate attention between interactive social partners with respect to objects or events in order to share an awareness of the objects or events (Mundy, Sigman, Ungerer, & Sherman, 1986). There is a range of joint attention behaviors that includes sharing attention (e.g., through the use of alternating eye gaze), following the attention of another (e.g., following eye gaze or a point), and directing the attention of another. Typically developing infants generally demonstrate all of these skills by 12 months of age (Carpenter, Nagell, & Tomasello, 1998), but some infants as young as 6 months display aspects of joint attention (e.g., matching direction of mother's head turn to a visible target; Morales et al., 1998).

The absence of joint attention ability has been unequivocally established as an early emerging and fundamental impairment in autism, present by 1 year of age in children wiht early-onset autism and incorporated into the diagnostic criteria for the disorder (American Psychiatric Association, 1994; Mundy et al., 1986). Through numerous studies, joint attention ability has been shown to distinguish preschool-age children with autism from those with developmental delays and typical development (Bacon, Fein, Morris, Waterhouse, & Allen, 1998; Charman et al., 1998; Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Mundy et al., 1986; Sigman, Kasari, Kwon, & Yirmiya, 1992). Joint attention skills have also been found to be a good predictor of both concurrent and future language skills in children with autism. In a longitudinal study of social competence and language skills in children with autism and Down syndrome, Sigman and Ruskin (1999) found that joint attention skills were concurrently associated with language ability for both groups and for the children with autism were predictive of long-term gains in expressive language skills. Using path analysis in a sample of 72 young children with autism, Dawson and colleagues found that social orienting ability was *indirectly* related to language ability through its contribution to joint attention skills. The authors hypothesized that a child's ability to attend to social information contributes critically to the acquisition of joint attention skills because such skills require the child to attend actively to social cues, particularly those expressed on the face (e.g., direction of eye gaze; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998). Other perspectives posit that it is a lack of a "shared attention mechanism" that is fundamentally responsible for the joint attention impairments seen in autism, rather than an impairment in attention to social stimuli (Baron-Cohen, 1995).

Attention to Others' Emotions

Another early emerging social behavior is noticing and responding to others' emotions. Infants within the first 6 months of life show great sensitivity to the emotions displayed by others (Trevarthen, 1979) and differentially respond to faces showing different emotions (e.g., neutral, happy, sad). Infants will attend longer and smile more frequently to a happy face as compared to a neutral or sad face (Rochat & Striano, 1999; Tronick, Als, Adamson, Wise, & Brazelton, 1978). Social referencing, whereby children seek emotional information from an adult's face when presented with a stimulus of uncertain valence, is established by 9–12 months of age (Feinman, 1982; Moore & Corkum, 1994). By 2 years of age, children begin to respond to another person's distress affectively and prosocially by helping, comforting, and sharing (Rheingold, Hay, & West, 1976; Zahn-Waxler & Radke-Yarrow, 1990).

Many, but not all, children with autism demonstrate a lack of sensitivity to the emotional states of others. Studies have shown that, when adults displayed facial expressions of distress, children with autism looked less at the adult and showed less concern compared to children with mental retardation and typical development (Bacon et al., 1998; Charman et al., 1998; Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Dawson, Toth, et al., 2004; Sigman et al., 1992). Further examination of these behaviors has shown that when a neutral affect condition was included, children with autism could distinguish between negative and neutral affect displays. Children with autism looked more at the examiner's face and showed more concern when the examiner showed a distressed expression than a neutral expression. However, they looked for shorter durations and showed less interest and concern in both conditions than did children with mental retardation (Corona, Dissanayake, Arbelle, Wellington, & Sigman, 1998).

Dawson and colleagues used event-related electrical brain potentials (ERPs) to examine whether young children with autism responded differentially to distinct emotional expressions. Differential ERPs to different facial expressions of emotion have been shown in adults (Eimer & Holmes, 2002), in typically developing children (de Haan, Nelson, Gunnar, & Tout, 1998), and even in infants as young as 7 months (Nelson & de Haan, 1996). To assess emotion perception skills in young children with autism, Dawson and colleagues showed 3- to 4-year-old children pictures of two facial expressions. In one picture the model's face depicted a neutral expression; in the other her face depicted a prototypic expression of fear (Dawson, Webb, et al., 2004). Compared to typically developing children, the children with autism exhibited significantly slower early (N300) brain responses to the facial expression of fear. Children with autism also failed to show a larger amplitude negative slow-wave response to the fearful face that characterized the ERPs of typically developing children. Moreover, the children with autism displayed aberrant ERP scalp topography in response to the fearful face. The delayed response to the fearful face suggests that information-processing speed is compromised, and the abnormal topography suggests a failure of cortical specialization or atypical recruitment of cortical areas in autism. Additionally, individual differences in N300 latency to the fearful face were associated with performance on behavioral tasks requiring social attention (tasks that were administered on a different day from ERP testing). The children with better joint attention skills, fewer social orienting errors, and who spent more time looking at an experimenter expressing distress displayed a faster N300 latency to the fearful face. In contrast, there was no association between N300 latency and performance on nonsocial tasks. These findings suggest that slower information-processing speed for emotional face stimuli is associated with more severe social attention impairments in children with autism.

Motor Imitation

The ability to imitate is a very early emerging and pivotal aspect of social development. Even newborns are capable of imitating facial expressions (Meltzoff & Moore, 1977, 1979, 1983), and imitation ability develops rapidly such that, by 1 year of age, infants are able to imitate actions on objects and gestures, such as waving. The imitation of observed actions later in new contexts, termed *deferred imitation*, emerges between the first and second year, although some researchers suggest that it develops much earlier (Meltzoff & Moore, 1994).

The importance of imitation in social development has long been recognized. Imitation has been proposed to serve as a basis for social connectedness with others as well as a basis for the child's ability to differentiate self from others (Eckerman, Davis, & Didow, 1989; Meltzoff & Gopnick, 1993; Nadel, Guerini, Peze, & Rivet, 1999; Trevarthen, Kokkinaki, & Fiamenghi, 1999; Užgiris, 1981). Imitation also promotes learning and understanding about the intentions and goals of others (Kugiumutzakis, 1999; Užgiris, 1999) and likely serves as a precursor for the development of a theory of mind (Meltzoff & Gopnick, 1993; Rogers & Pennington, 1991). Imitation also plays a role in symbolic play (Piaget, 1962), peer relationships (Trevarthen al., 1999), language (Avikainen, Wohlschlager, Liuhanen, Hanninen, & Hari, 2003; Charman et al., 2003), and emotional sharing (Hatfield, Cacioppo, & Rapson, 1994).

A failure to spontaneously imitate others, especially in social play contexts, appears to be a core early impairment in autism (Dawson & Adams, 1984; Dawson & Lewy, 1989; Rogers, Bennetto, McEvoy, & Pennington, 1996; Rogers & Pennington, 1991; Williams, Whiten, Suddendorf, & Perrett, 2001). Imitation ability discriminates toddlers with autism from those with mental retardation or a communication disorder (Stone, Lemanek, Fishel, Fernandez, & Altemeier, 1990; Stone, Ousley, & Littleford, 1997). Numerous studies have demonstrated that individuals with autism perform poorly in virtually all aspects of imitation (Rogers, Hepburn, Stackhouse, & Wehner, 2003), including imitating motor movements (Hertzig, Snow, & Sherman, 1989), facial expressions (Loveland et al., 1994), the style of tasks (Hobson & Lee, 1999), actions involving imaginary objects (Rogers et al., 1996), and vocalizations (Dawson & Adams, 1984).

Williams and colleagues (2001) hypothesize that the imitation deficits observed in autism are the result of a deficit in self–other mapping. That is, imitation deficits reflect an impairment in the ability to map the complex actions of others onto a reference for the self. Meltzoff and colleagues (Meltzoff & Decety, 2003; Meltzoff & Gopnick, 1993) have proposed a similar concept in the "Like Me" hypothesis.

Face Processing

Faces have special significance and provide nonverbal information important for communication for typically developing infants (Darwin, 1872/1965). Face recognition ability is present very early in life. Indeed, at birth, neonates show the capacity for very rapid face recognition (Walton & Bower, 1993) and a visual preference for faces (Goren, Sarty, & Wu, 1975). By 4 months, infants recognize upright faces better than upside down faces (Fagan, 1972) and by 6 months, infants show differential ERPs to familiar versus unfamiliar faces (de Haan & Nelson, 1997, 1999). By the end of the first year of life, infants are capable of differentiating facial gestures, determining the direction of eye gaze, and attending to expressions of emotion. These early developing abilities, particularly attention and response to the face and gaze, are essential to successful joint attention and social orienting interactions. Face processing has also been suggested to be important in the development of social relationships and theory of mind (Baron-Cohen, 1995; Brothers, Ring, & Kling, 1990; Perrett, Harries, Mistlin, & Hietanen, 1990; Perrett, Hietanen, Oram, & Benson, 1992; Williams et al., 2001).

Face processing abilities in individuals with autism have consistently been shown to be impaired. In a retrospective study using videotapes of first birthday parties, the failure to look at others was the single best discriminator between infants who were later diagnosed with an autism spectrum disorder and those with typical development (Osterling & Dawson, 1994; see also Adrien et al., 1991). In a case study published by Dawson and colleagues (Dawson, Osterling, Meltzoff, & Kuhl, 2000), a young infant who was diagnosed with autism at 1 year of age and rediagnosed at 2 years of age was reported to show atypical eye contact. In early medical records chronicling his first 6 months, he reportedly demonstrated "generally good eye contact, although at times he averted his eyes" and smiled responsively. However, on four different evaluations from 9 to 13 months, his eye contact was reported as "a transfixed stare," "poor," and "within normal limits." Thus, the infant's use of eye gaze appeared to develop normally at first, becoming variable and typical only during the second half of the first year of postnatal life. Reportedly, during this same period, the infant showed reduced social responsiveness, and social interactions were described as "aversive" to the infant.

Using ERPs Dawson, Carver, and colleagues (2002) examined face recognition abilities in 3- to 4-year-old children with autism, developmental delay, and typical development. In this study, high-density ERPs were recorded from the children while they watched images of familiar (mother) and unfamiliar (another female) faces and familiar (favorite toy) and unfa-

miliar (novel toy) objects. The typical children demonstrated increased amplitude to the novel faces and objects for two ERP components. The children with autism showed the same differential ERP response for the objects, but did not show the differential response for the faces. These findings indicate that children with autism demonstrate selective face recognition impairments as early as 3 years of age.

Studies of face memory in autism have shown that by middle childhood, children with autism perform worse than mental-age- and chronological-age-matched peers on a number of face processing tasks. These tasks include tests of both face recognition (Boucher & Lewis, 1992; Boucher, Lewis, & Collis, 1998; Gepner, de Gelder, & de Schonen, 1996; Klin et al., 1999) and face discrimination (Tantam, Monoghan, Nicholson, & Stirling, 1989). Whereas typically developing children show better memory performance for faces than non-face visual stimuli, children with autism perform comparably on face and non-face tasks (Serra et al., 2003) or show better performance on non-face tasks (e.g., memory for buildings) than on face tasks (Boucher & Lewis, 1992). Studies also suggest that individuals with autism process faces using abnormal strategies. By middle childhood, typically developing children (1) are better at recognizing parts of a face when the parts are presented in the context of a whole face, (2) perform better when recognition involves the eyes versus the mouth (Joseph & Tanaka, 2003), (3) show a greater decrement in memory for inverted versus upright faces as compared with non-face visual stimuli, and (4) attend to upright faces for longer lengths of time than inverted faces (van der Geest, Kemner, Verbatem, & van Engeland, 2002). In contrast, children with autism are better at recognizing isolated facial features and partially obscured faces than typical children (Hobson, Ouston, & Lee, 1988; Tantam et al., 1989) and show better memory performance for the lower half of the face than the upper half during childhood (Langdell, 1978). Other studies of visual attention to faces indicate that individuals with autism exhibit reduced attention to the core features of the face, such as the eyes and nose, relative to typical individuals (Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Pelphrey et al., 2002; Trepagnier, Sebrechts, & Peterson, 2002).

HYPOTHESES REGARDING THE NEURAL BASIS OF EARLY SOCIAL IMPAIRMENTS IN AUTISM

As reviewed above, autism is associated with a wide range of early impairments in social behavior. We now address the question of what the neurodevelopmental basis of such impairments in autism might be. We describe a general model of the emergence of social brain circuitry in the

first year of life and discuss how the trajectory of normal development of social brain circuitry is altered in autism.

At least two alternatives can be offered to explain the early social impairments found in autism. The first is that there might exist basic perceptual–cognitive impairments. For example, these might be deficits in general abilities that are important for face processing, such as the ability to perceptually bind features of a stimulus (Dawson, Webb, et al., 2002) or to form prototypes (Klinger & Dawson, 2001), or deficits in specific neural mechanisms that are specialized for processing social information, such as the fusiform gyrus for faces (Haxby et al., 1994, 1999; Hoffman & Haxby, 2000; Kanwisher, McDermott, & Chun, 1997) or the superior temporal sulcus for eye movements (Perrett et al., 1985, 1992; see also Pelphrey & Carter, Chapter 3, this volume). A primary perceptual deficit would impact other aspects of social brain circuitry, especially those aspects that rely on social perception, such as joint attention, interpretation of emotional expression, and even speech perception.

The second hypothesis, referred to as the *social motivation hypothesis*, posits a primary impairment in social motivation—that is, the affective tagging of socially relevant stimuli (Dawson, Webb, & McPartland, 2005; Dawson, Carver, et al., 2002; Grelotti, Gauthier, & Schultz, 2002; Waterhouse, Fein, & Modahl, 1996). The evidence for a social motivation impairment in autism comes from both clinical observations and research findings. Clinically, diagnostic criteria for autism include "a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people" and "lack of social or emotional reciprocity" (American Psychiatric Association, 1994). Dawson, Hill, Galpert, Spencer, and Watson (1990) found that preschool-age children with autism were less likely to smile when looking at their mothers during social interaction, and young children with autism have been found to be less likely to express positive emotion during joint attention episodes (Kasari, Sigman, Mundy, & Yirmiya, 1990).

According to this hypothesis, reduced social motivation results in less time spent paying attention to faces as well as to all other social stimuli, such as the human voice, hand gestures, and so forth. Previously, Dawson hypothesized that social motivational impairments in autism are related to a difficulty in forming representations of the reward value of social stimuli (Dawson, Carver, et al., 2002). One of the primary neural systems involved in processing reward information is the dopamine system (Schultz, 1998). Dopaminergic projections to the striatum and frontal cortex, particularly the orbitofrontal cortex, are critical in mediating the effects of reward on approach behavior. The orbitofrontal cortex, which is dependent on input from the basolateral amygdala, is implicated in the formation of representations of reward value (Schoenbaum, Setlow, Saddoris, & Gallagher,

2003). The dopamine reward system is activated in response to social rewards, including eye contact (Kampe, Frith, Dolan, & Frith, 2001). Gingrich, Liu, Cascio, Wang, and Insel (2000) showed that dopamine D2 receptors in the nucleus accumbens are important for social attachment in voles. Dawson, Munson, and colleagues (2002) reported that performance on neurocognitive tasks that tap the medial temporal lobe–orbitofrontal circuit (e.g., object discrimination reversal) is strongly correlated with the severity of joint attention impairments in young children with autism. We hypothesize that dysfunction of the dopamine reward system, especially its functioning in social contexts, might account for impairments in social motivation found in autism.

Oxytocin and Its Relation to the Dopamine Reward System

Waterhouse and colleagues (1996) hypothesized that impaired functioning of the oxytocin system in autism reduces social bonding and affiliation. Insel (1997) has discussed the role of peptides, specifically oxytocin and vasopressin, in the modulation of the dopamine reward circuit in social contexts. These peptides play an important role in linking social input to the reinforcement system (Pedersen et al., 1994). Several animal studies have shown that vasopressin and oxytocin are critical in facilitating "social memory." For example, oxytocin knockout mice show a profound and specific deficit in social memory (Ferguson, Young, Hearn, Insel, & Winslow, 2000; Ferguson, Young, & Insel, 2002; Nishimori et al., 1996). These knockout mice studies provide support for the notion that social memory has a neural basis distinct from other forms of memory. Interestingly, during the initial exposure to a familiar conspecific, oxytocin acts in the medial amygdala to facilitate social recognition. Indeed, both oxytocin and vasopressin appear to play a role in a variety of social behaviors, including social affiliation (Witt, Winslow, & Insel, 1992), maternal behavior (Pedersen et al., 1994), and social attachment (Insel & Hulihan, 1995; Winslow, Hastings, Carter, Harbaugh, & Insel, 1993). Insel and Fernald (2004) suggest that these peptides may operate on social behavior through their influence on the mesocorticolimbic dopamine circuit that links the anterior hypothalamus to the ventral tegmental area and the nucleus accumbens. This circuit may be especially important for mediating sensitivity to social reward in the context of social interaction.

We hypothesize that reduced reward value ("emotional tagging") of social stimuli may result in the profound social impairments found in individuals in autism as well as contribute to the language processing impairments characteristic of the disorder. Like Insel, O'Brien, and Leckman

(1999), we speculate that this factor might be related to abnormalities in peptides such as oxytocin and/or vasopressin, which modulate the dopamine reward pathway, specifically in the context of social interactions. In fact, there is some evidence of abnormalities in oxytocin and vasopressin in autism. In one study, reduced plasma concentrations of oxytocin were found in children with autism (Modahl et al., 1998). In another, Kim and colleagues (2002) found a nominally significant transmission disequilibrium between autism and an AVPR1A microsatellite, a V_{1a} receptor in the brain that has been shown to mediate the action of vasopressin. Clearly, this is an interesting area for future research in autism.

Emergence of Social Brain Circuitry in the First Year of Life

Dawson, Webb, and colleagues (2005) have described a developmental model for the normal emergence of social brain circuitry during early infancy, stressing the key role of the reward system in the development of the social brain (see Figure 2.1). In the model, drawing upon the work of Insel and colleagues (1999), modulation of the dopamine reward circuit by oxytocin is important for shaping the infant's early preference for social stimuli and attention to such stimuli. As mentioned above, in normal development, neonates display a particular attraction to people, especially to the sounds, movements, and features of the human face (Maurer & Salapatek, 1976; Morton & Johnson, 1991). Spontaneous orienting to a social stimulus, such as head turning when one's name is called, can be seen in infants by about 6–7 months of age.

We hypothesize that volitional orienting occurs, in part, because the infant anticipates pleasure (reward) to be associated with such stimuli. This type of interaction involves activation of the reward circuit, including parts of the prefrontal regions, such as the orbital prefrontal cortex, that play a role in the formation of reward representations. With increasing experience with faces and voices, which occurs in the context of social interactions, cortical specialization for faces and linguistic stimuli develops. This specialization involves the fine-tuning of perceptual systems. Furthermore, areas specialized for the perceptual processing of social stimuli, such as the fusiform gyrus and superior temporal sulcus, become tightly integrated with regions involved in reward (e.g., amygdala) as well as regions involved in motor actions and attention (e.g., cerebellum, prefrontal/cingulate cortex). Through this integration process, increasingly complex social brain circuitry emerges. In turn, this developing circuitry supports more complex behaviors, such as disengagement of attention, joint attention, intentional communication, and delayed imitation.

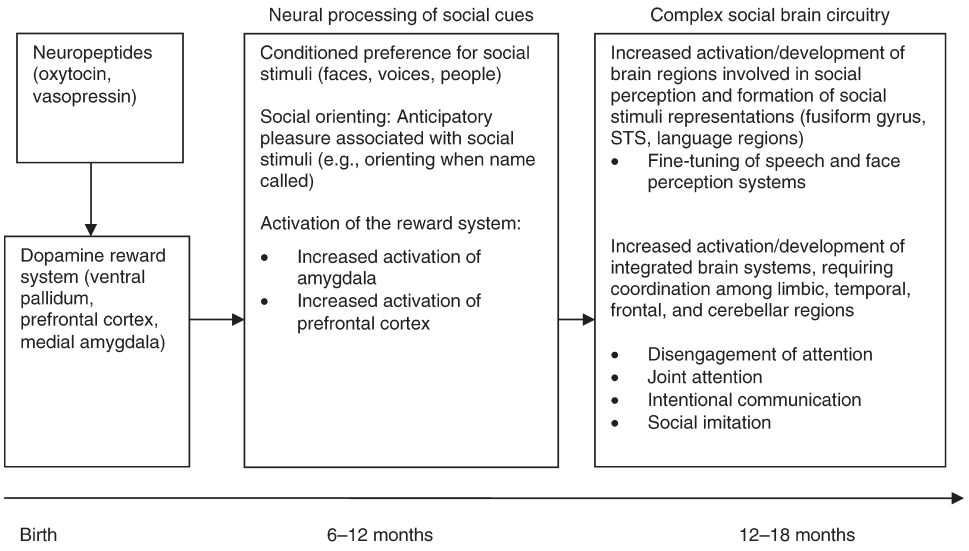

FIGURE 2.1. The role of social reward in the emergence of social brain circuitry in the first years of life. Reproduced with permission from Dawson, G., et al. (2005). Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism. *Development and Psychopathology, 17*, 679–697.

Implications for Autism

One of the earliest symptoms of autism is a lack of "social orienting" (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Dawson, Toth, et al., 2004). This reduced attention to social stimuli and concomitant reduced experience with social stimuli likely results in a failure to become an expert face and language processor (Dawson et al., 2005; Grelotti et al., 2002). Because experience drives cortical specialization (Nelson, 2001), reduced attention to faces and speech would lead to a failure of specialization of brain regions that typically mediate face and language processing. This failure would be reflected in decreased cortical specialization and abnormal brain circuitry for face processing, resulting in slower information-processing speed. In two ERP studies (McPartland, Dawson, Webb, & Panagiotides, 2004; Webb, Dawson, Bernier, & Panagiotides, 2006), young children as well as adolescents and adults with autism exhibited slower ERPs to faces and failed to show the normal right lateralization of ERPs to faces relative to well-matched comparison groups. These studies

suggest that autism is associated with both slower information-processing speed and atypical cortical specialization for face processing.

The abnormal trajectory for brain development in autism is not caused by a simple lack of exposure to human faces and voices. Infants with autism, like typically developing infants, are held, talked to, and fed by their parents during face-to-face interactions. However, if the infant with autism does not find such interactions inherently interesting or rewarding, then the infant might not actively attend to the face and voice or perceive the face within a larger social–affective context. Recent research suggests that simple exposure to language does not necessarily facilitate the development of brain circuitry specialized for language (Kuhl, Tsao, & Liu, 2003). Rather, for speech perception to develop, language needs to be experienced by the infant within a socially interactive context. Very early in life, infants are capable of discerning differences among the phonetic units of all languages, including both native and foreign languages. However, between 6 and 12 months of age, as the brain becomes proficient at speech perception, the ability to discriminate foreign language phonetic units declines (Kuhl et al., 1997). Kuhl and colleagues (2003) investigated the possibility of preventing this decline in foreign language phonetic perception by exposing American infants to native Mandarin Chinese speakers. They found that the decline of foreign language phonetic perception was preventable, *but only if exposure to speech occurred in the context of interpersonal interaction*. That is, an experimental condition in which infants were exposed to the same speech stimuli via audiotapes without social interaction did not avoid the narrowing of speech perception for the non-native language.

In the case of autism, if the child is not *actively attending to* faces and speech sounds as part of the social context, his or her early exposure to these social stimuli might not facilitate face and speech perception. The results of a recent study are consistent with this notion. Kuhl, Coffey-Corina, Padden, and Dawson (2004) found that listening preferences in 3- to 4-year-old children with autism differed dramatically from those of typically developing children. The children with autism preferred listening to mechanical-sounding auditory signals (computer-based signals acoustically matched to speech) rather than speech (motherese). The preference for the mechanical-sounding stimuli was associated with lower language ability, more severe autistic symptoms, and abnormal ERPs to speech sounds. The children with autism who did prefer motherese were more likely to show differential ERPs to different phonemes, whereas those who preferred the mechanical-sounding signal showed no such ERP waveform differences. We hypothesize that a failure to affectively tag social and linguistic stimuli as relevant and rewarding, and the resultant failure to attend to such stimuli, impedes the cortical specialization for brain regions typically associated with face and language processing. Therefore, perceptual fine-tuning of such social stimuli and

the formation of representations of these stimuli are hampered. As a result, more complex behaviors that require the integration of social stimuli with coordinated, intentional movements and volitional attention, such as disengagement of attention and joint attention, then fail to emerge.

Potential Impact of Early Intervention

If the social motivation hypothesis is correct, it should be possible to alter children's attention to, and experience with, faces and speech through early intervention aimed at making social interactions more rewarding and meaningful. The impact of such an intervention on the development of face processing could then be assessed by examining the brain's responses to faces by using ERPs (Dawson & Zanolli, 2003). Through intervention, children can increase their use of eye contact, their use of affective exchanges, and their joint attention skills. An increase in these behavioral skills may be related to improvements such as increasing specialization in the neural face processing system. Indeed, interventions based on applied behavior analysis are designed to enhance the reward value of social stimuli through learning principles (see Figure 2.2). For example, during most early intervention programs, the therapist's face (a previously neutral stimulus) is deliberately paired with a nonsocial reinforcer (usually access to food or a toy). Via classical conditioning, the face then acquires reinforcer value. Early intervention could facilitate the development of the face processing system in two ways: first, by helping the child engage in meaningful social interactions that might lead to active attention to faces, and second, by altering the child's motivational preferences for faces so that engaging in face-to-face interaction becomes more rewarding and therefore more frequent (Dawson & Zanolli, 2003).

The timing of intervention might also have important consequences in relation to the plasticity of the face processing system. Increases in social motivation and active attention to faces might have differing results in children as compared to adults. For example, adults with autism might benefit from being trained to attend to faces and being taught explicit face processing strategies. However, although these interventions might result in better behavioral performance, it is unclear if they would result in alterations in patterns of neural activation. That is, interventions might support compensatory processes but fail to activate or develop typical processing mechanisms. Conversely, given the plasticity of the developing brain, young children who receive early intervention might demonstrate both improved behavioral performance (e.g., increases in eye contact, joint attention, and face recognition) as well as normalized brain functioning. This normalized brain functioning could be observed in differential responses to familiar versus unfamiliar faces, different phonemes, speed of neural responses, and

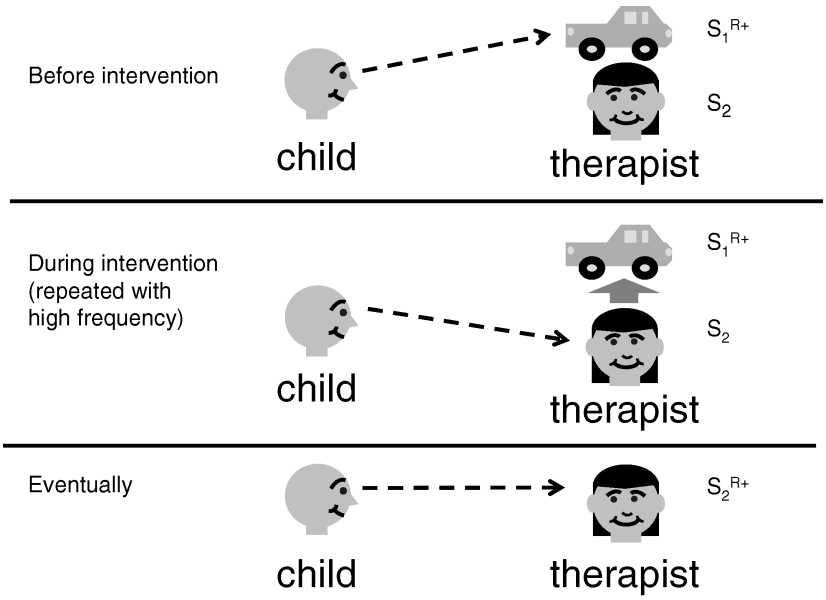

FIGURE 2.2. A model of the acquisition of social motivation in autism. Reproduced with permission from Dawson, G., & Zanolli, K. (2003). Early intervention and brain plasticity in autism. In G. Bock & J. Goode (Eds.), *Autism: Neural bases and treatment possibilities* (pp. 266–280). Chichester, UK: Wiley.

patterns of cortical specialization, as reflected in scalp topography and latency of ERP components during face and language processing tasks. Dawson is currently examining this possibility in an NIMH-funded randomized clinical trial of early intensive (25–30 hours a week for 2 years) behavioral intervention for toddlers with autism. The intervention combines both traditional applied behavior analytic strategies with more play-based approaches that emphasize the affective relationship between the child and his or her partner. We theorize that the emphasis on affective reciprocity is important for addressing the social motivational deficits found in autism, which, as argued above, theoretically affect how representations for social and language stimuli are acquired and stored.

EVIDENCE FOR A GENETIC BASIS OF SOCIAL IMPAIRMENTS IN AUTISM

We conclude by describing recent evidence for a genetic basis for social impairments in autism. Studies of typical individuals are beginning to link specific genes to aspects of social behavior (Bertolino et al., 2005; Brown et

al., 2005; Hariri et al., 2005), but autism risk genes have yet to be identified. However, evidence for a genetic basis of autism does exist. There is strong evidence for genetic influence in autism, with estimates of heritability ranging from 91–93% (Bailey et al., 1995). Several studies have shown that identical twins are 60–95% concordant for autism (Bailey et al., 1995; Folstein & Rutter, 1977; Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985; Steffenburg et al., 1989), whereas fraternal twins and siblings have a much lower concordance rate, with estimates ranging from 3–7% (August, Stewart, & Tsai, 1981; Bailey et al., 1995; Bolton et al., 1994; Smalley, Asarnow, & Spence, 1988). This rapid decrease in risk rates from identical twins to siblings and differential risk rates for male versus female siblings suggest epistatic effects involving interactions among as many as 10 or more genes (Delong & Dwyer, 1988; Jorde, Mason-Brothers, Waldmann, & Ritvo, 1990; Pickles et al., 1995; Risch et al., 1999; Smalley et al., 1988). Several linkage studies have reported moderate positive signals on several chromosomes; however, findings have not been strongly consistent across these studies.

One challenging issue for genetic studies is the complex phenotype that comprises the autism syndrome. The disorder involves at least three different symptom domains (social, communication, and restrictive behaviors/flexibility) and its presentation is extremely heterogeneous. Furthermore, the autism phenotype appears to extend beyond classic autism to "lesser variant" phenotypes, referred to as the "broader autism phenotype" (Rutter, Bailey, Bolton, & Le Couteur, 1993). Numerous studies have shown that relatives of individuals with autism, including parents and siblings, exhibit higher than normal rates of autism-related impairments (Bailey et al., 1995; Bailey, Phillips, & Rutter, 1996; Baker, Piven, Schwartz, & Patil, 1994; Bolton et al., 1994; Landa, Folstein, & Isaacs, 1991; Landa et al., 1992; Narayan, Moyes, & Wolff, 1990; Wolff, Narayan, & Moyes, 1988). For example, Piven and colleagues (Piven, Palmer, Jacobi, Childress, & Arndt, 1997; Piven, Palmer, Landa, et al., 1997) found that parents of two or more children with autism showed elevated rates of social and communication impairments and stereotyped behaviors, and Bolton and colleagues (1994) reported that 10–20% of siblings of individuals with autism exhibit symptoms related to the disorder, including language, learning, communication, and social impairments.

To date, most linkage studies have characterized the autism phenotype in terms of qualitative discrete diagnoses. However, it is likely that autism susceptibility genes increase the chance of developing one or more components of the syndrome rather than causing autism, per se. In theory, it might be the case that multiple genetically related traits accumulate to cross a threshold into the full-blown syndrome autism. If so, in order to identify the genes related to autism it would be essential to define these genetically

related traits, or endophenotypes, and determine their association with specific genes (Dawson, Webb, et al., 2002; Holden, 2003). Such biological or behavioral markers of latent vulnerability to autism are likely not discrete, all-or-nothing characteristics, but rather continuously distributed traits.

There have been few genetic studies that have attempted to measure autism-related traits along a continuum. Constantino and colleagues (Constantino, Przybeck, Friesen, & Todd, 2000; Constantino, Davis, et al., 2003) conducted one such study by developing a questionnaire that captured autism as one continuous trait. They found evidence for a genetic basis of this trait in twin studies (Constantino, Hudziak, & Todd, 2003; Constantino & Todd, 2000, 2003). More recently, Dawson and colleagues (2006) have developed a quantitative measure of the autism broader phenotype that separately assesses several distinct domains of autism symptoms (social motivation, social expressiveness, conversation skills, and restrictive behaviors/flexibility) as well as age of language onset. The Broader Phenotype Autism Symptom Scale (BPASS) assesses autism-related traits in both parents and siblings of children with autism through interview and direct observation of behaviors. Parents are interviewed about their own functioning or the functioning of their children and observations of both parent and child are made by the interviewer through direct interactions. Nonverbal behaviors, such as eye contact, are assessed via direct observation, whereas behaviors related to restricted activities and routines are assessed via interview. A genetic investigation of these quantitative traits was conducted using BPASS data collected on a sample of 201 autism multiplex families that included 694 individuals (Sung et al., 2005). Participants included parents, probands, and nonaffected siblings from nuclear families that had at least two children on the autism spectrum. Multivariate polygenic models with ascertainment adjustment to estimate heritabilities and genetic and environmental correlations between the traits were used. Among the traits analyzed, social motivation and restricted activities/flexibility showed the highest heritability (0.19 and 0.16, respectively), indicating that these traits may be promising for gene mapping. These two traits also showed strong genetic correlation (0.92), suggesting a shared genetic basis.

Interestingly, in studies of face processing, not only children with autism but also parents of children with autism show decrements in this skill (Dawson, Webb, et al., 2005). Viewing faces typically is associated with a faster and larger negative ERP component over the right temporal region at about 170 milliseconds (ms) poststimulus presentation (this face-sensitive ERP is referred to as the N170; Bentin, Allison, Puce, Perez, & McCarthy, 1996; Kanwisher et al., 1997). As mentioned previously, it was found that the N170 was atypical in individuals with autism: They did not exhibit the expected N170 latency advantage for faces as compared to nonface stimuli, and they showed bilateral rather than right lateralized ERP

responses to faces (McPartland et al., 2004). Dawson, Webb, and colleagues (2005) examined performance of parents of children with autism on standardized Wechsler cognitive tasks assessing verbal (Vocabulary, Verbal Comprehension), visual spatial (Block Design, Object Assembly), and face recognition (Immediate Memory for Faces) abilities. It was found that the parents of children with autism showed a significant deficit on the face recognition task relative to their performance on the visual spatial and verbal tasks; in fact, 29% of the sample had face recognition scores that were 1 standard deviation (SD) lower (> 3 points) than the other cognitive tasks. High-density ERPs to faces and chairs were recorded from a subset of the parents of children with autism and control adults with no familial history of autism. Control adults demonstrated the expected larger right-than-left hemisphere N170 to faces, whereas parents of children with autism demonstrated reduced right hemisphere N170 amplitude to faces, resulting in bilaterally distributed ERPs to faces. Furthermore, control adults exhibited the expected pattern of a faster N170 to upright faces than upright chairs, whereas parents of children with autism showed no significant difference in N170 latency to upright faces versus upright chairs. Based on these results, it can be hypothesized that face processing might be a functional neural trait marker of genetic susceptibility to autism.

Although these initial studies suggest that quantitative analysis of autism symptom-related traits is a promising approach for genetic studies, ultimately, a more refined measure of functional neural trait markers—one that is informed by contemporary affective and social neuroscience—will likely yield greater precision and validity. Through the discovery of autism susceptibility genes, it may someday be possible to identify newborn infants at risk for autism, allowing for very early intervention. By providing appropriate stimulation during the early years when social brain circuitry is first developing, prevention or at least meaningful amelioration of symptoms of autism might eventually be possible, especially for children without significant comorbid mental retardation. As our understanding of the development of social brain circuitry evolves, our interventions can become more targeted and focused on those aspects of social behavior that are considered fundamental and pivotal for the acquisition of more complex social and communication skills over time.

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