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Neurobiological correlates of social functioning in autism

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ABSTRACT

Although autism is defined by deficits in three areas of functioning (social, communicative, and behavioral), impairments in social interest and restricted behavioral repertoires are central to the disorder. As a result, a detailed understanding of the neurobiological systems subserving social behavior may have implications for prevention, early identification, and intervention for affected families. In this paper, we review a number of potential neurobiological mechanisms—across several levels of analysis—that subserve normative social functioning. These include neural networks, neurotransmitters, and hormone systems. After describing the typical functioning of each system, we review available empirical findings specific to autism. Among the most promising potential mechanisms of social behavioral deficits in autism are those involving neural networks including the amygdala, the mesocorticolimbic dopamine system, and the oxytocin system. Particularly compelling are explanatory models that integrate mechanisms across biological systems, such as those linking dopamine and oxytocin with brain regions critical to reward processing.

Contents

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1. Introduction

Of all childhood psychiatric disorders, autism is among the most pervasive and earliest to emerge. Diagnostic criteria for autism include three broad areas of impairment (American Psychiatric Association, 2000). The first relates to social interaction, including deficits in expression and gesture, social and emotional reciprocity, and sharing of interest. A second area of impairment is in communication, including deficits in behaviors ranging from spoken language to symbolic play. The third includes restricted and stereotyped behavior, interests, and activities, and encompasses rigid preferences for routine as well as repetitive motor mannerisms. Although the features of autism are often referred to as a "triad of impairment" (Wing, 1981), social impairments may be foundational, as longitudinal studies suggest that early social deficits provide near perfect classification of later diagnosis (Dawson & Bernier, 2007; Osterling & Dawson, 1994). The term 'autism spectrum disorder' (ASD) is often used to encompass classic autism, Asperger's disorder, and pervasive developmental disorder not otherwise specified (PDDNOS; Dawson & Faja, 2008), and thus the diagnosis is characterized by a great deal of heterogeneity. Although autism is often considered a disorder of childhood due to the diagnostic requirement of impairment by age three, its effects persist throughout the lifespan.

Family studies reveal a strong genetic component for ASDs. Concordance among monozygotic twins ranges between 69 and 95%, whereas concordance among dizygotic twins ranges from 0 to 24% (Bailey et al., 1995; Folstein & Rutter, 1977; Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985; Steffenburg et al., 1989). However, despite the high heritabilities found in behavioral genetics studies, specific genes involved in the etiology of ASD have been elusive, although it is clear that the disorder is polygenic (Dawson & Faja, 2008). At present, some candidate genes include the serotonin transporter (5-HTT), engrailed 2 (En-2), and the oxytocin receptor (OXTR; Bartz & Hollander, 2008; Dawson, 2008). To date, much work remains to elucidate genetic characteristics of ASD, as well as biomarkers and endophenotypes that indicate specific genetic risk.

1.1. Core social deficits

Before considering the biological bases of social impairments in ASD, it is useful to characterize such impairments behaviorally. Dawson and Bernier (2007) describe five particular areas of social functioning in which individuals differ from age-matched controls as early as preschool. The first, social orienting, refers to a tendency to direct attention spontaneously toward social stimuli (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998). Whereas typically developing children demonstrate attraction to social stimuli shortly after birth, children with ASD are less likely to look preferentially or orient toward social stimuli (e.g., hands clapping and a voice calling their name) than are controls (Osterling & Dawson, 1994; Swettenham et al., 1998).

Such deficits in social orienting are likely responsible in part for the second area of social impairment, joint attention (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998). The ability to share awareness with others by sharing, following, and/or directing attention typically emerges during the first year of life (Mundy, Sigman, Ungerer, & Sherman, 1986), and supports the development of subsequent linguistic and social skills (Dawson et al., 2004; Toth, Munson, Meltzoff, & Dawson, 2006). Children with ASD show well-documented deficits in both initiation and following of joint attention, even after accounting for deficits in social orienting more generally (Colombi et al., 2009; Leekam, López, & Moore, 2000; Leekam & Ramsden, 2006; Naber et al., 2008; Sullivan et al., 2007).

Intertwined with both social orienting and joint attention is processing of facial information, the third area of difficulty (Dawson & Bernier, 2007). Whereas typically developing infants look preferentially toward human faces with in the first minutes after birth (Goren, Sarty, & Wu, 1975), lack of attention to faces is among the earliest indicators of ASD (Osterling, Dawson, & Munson, 2002; Osterling & Dawson, 1994). Both children and adults with ASD use less holistic face processing strategies, placing relatively greater emphasis on featural (as opposed to configural) information (Deruelle, Rondan, Gepner, & Tardif, 2004; Rosset et al., 2008), and may also prioritize information from the mouth over that of the eyes, resulting in decreased accuracy and efficiency relative to controls during tasks of race recognition or matching based on expression, gaze direction, or sex (Deruelle et al., 2004; Joseph & Tanaka, 2003; Klin, Jones, Schultz, Volkmar, & Cohen, 2002).

A fourth area of impairment is in motor imitation. Typically, infants are able to imitate others from a very young age, perhaps as early as a few weeks (Meltzoff & Moore, 1977). By the end of their first year, they are able to imitate behavior selectively and flexibly based upon complex social cues (Nielsen & Carpenter, 2008). Children with ASD, in contrast, show deficits in spontaneous and prompted imitation of basic hand, facial, and body movements, as well as simple actions on objects (Colombi et al., 2009; Rogers, Hepburn, Stackhouse, & Wehner, 2003). They are also less likely to imitate the style with which an action is performed (Hobson & Hobson, 2008) and do not discriminate between "accidental" and "intentional" actions in their imitation, unlike children without the disorder (D'Entremont & Yazbek, 2007).

The final dimension of social deficit involves the degree to which individuals with ASD respond to emotional cues from others (Dawson & Bernier, 2007). At a basic level, those with ASD display difficulties in recognition of emotions based on visual and vocal cues (Golan, Baron-Cohen, Hill, & Golan, 2006). Interpersonally, individuals with ASD react differently to displays of distress by others (Sigman, Dissanyake, Corona, & Espinosa, 2003). In a number of studies assessing response to a feigned injury and consequent distress expressed by an experimenter, children with ASD looked less at the experimenter's face and supposed injury (Corona, Dissanayake, Arbelle, Wellington, & Sigman, 1998; Dawson et al., 2004). Children with ASD are also less likely than controls to provide a prosocial response during similar help-seeking paradigms (Bacon, Fein, Morris, Waterhouse, & Allen, 1998).

1.2. Scope of the current paper

Following from this brief review, our goal in writing this paper is to review biological systems thought to subserve social functioning among individuals with and without ASD. From the discussion thus far, it is clear that ASD is characterized by early and pervasive deficits in social behavior. It is important to identify biological substrates of social functioning in ASD (and other disorders), as such knowledge may facilitate efforts at early detection, prevention, and intervention (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008). The following discussion is organized around multiple neurobiological levels of analysis that affect social behavior, including neural and hormonal influences. For each, we will focus on (1) functioning in the general population, and (2) functioning among individuals with ASD. As will become evident, the extent to which each system has been explored in ASD varies significantly. As a result, conclusions in many areas are premature and necessarily tentative.

2. The "social brain"

Nearly 20 years ago, Brothers (1990) identified a network of brain structures that have come to be known as the "social brain" (Zilbovicius et al., 2006). This network facilitates social cognition and behavior across a range of functions of varying complexity. Although the label "social brain network" is a useful heuristic by which to refer to these brain regions, it is somewhat misleading in that it exaggerates their functional specificity. Nonetheless, the network of structures and regions discussed below are central to social functioning. Typically

included are the superior temporal sulcus, the fusiform gyrus, the amygdala, the prefrontal cortex (PFC), and areas comprising the mirror neuron system. Each of these regions is discussed below, including both structural and functional findings as available.

2.1. Superior temporal sulcus

The superior temporal sulcus (STS) plays an important role in social perception, which has been defined as the processing of socially-relevant sensory information (Zilbovicius et al., 2006). Adolphs (2003) proposes a hierarchy of processing in this domain, in which the STS and fusiform gyrus perform detailed perceptual processing of social information, which is then assigned an emotional value by subcortical structures including the amygdala and the ventral striatum, and by cortical structures including the orbitofrontal cortex (OFC). Consistent with this theory, findings among nonclinical samples implicate the STS in the processing of a number of different types of sensory information relevant to social interaction. First, the STS displays selective sensitivity to vocal and speech stimuli over nonsocial auditory stimuli. In a series of studies, Belin, Zatorre, Lafaille, Ahad, and Pike (2003) found that sensitivity to human voice sounds peaked along the upper bank of the central area of the STS, particularly in the right hemisphere, and activation was specific to vocal sounds compared to various categories of non-vocal sounds. The STS also differentiates between different individuals' voices (Belin & Zatorre, 2003), and within the STS, particular regions appear to facilitate different aspects of voice processing. Voice recognition in general activates the anterior STS, whereas recognition of unfamiliar voices activates the posterior STS more strongly (Kriegstein & Giraud, 2004).

The STS is equally important in processing biological motion of the hands, face, eyes, and body (Zilbovicius et al., 2006), particularly as it relates to emotional expression, eye gaze, and intentional inference (LaBar, Crupain, Voyvodic, & McCarthy, 2003; Andrews & Ewbank, 2004). Shifts in eye gaze elicit STS activation as early as middle childhood (Mosconi, Mack, McCarthy, & Pelphrey, 2005). Perception of intentional information presented with a finger point increases activation in the posterior STS (Materna, Dicke, & Thier, 2008), as does inference of intention to moving geometric shapes (Schultz, Imamizu, Kawato, & Frith, 2004) and tasks which require “mentalizing”, or making attributions of intentions or goal-directed behaviors among others (Spiers & Maguire, 2006). Thus, commonalities among tasks that recruit the STS indicate that it is critical in the perception and processing of social information across modalities (Materna et al., 2008; Redcay, 2008).

Consistent with parallels between the behavioral features of autism and the role of the STS, there is compelling evidence of both structural and functional abnormalities within the STS among individuals with ASD. Compared to controls, adults with ASD display differences in grey matter volumes throughout frontal and temporal regions (Abell et al., 1999). Among children with ASD, STS grey matter is reduced bilaterally, with decreased white matter concentrations in the right pole of the temporal lobe and an anterior shift in the location of the STS relative to controls (Boddaert et al., 2004; Levitt et al., 2003). Individuals with ASD also display cortical thinning of the STS (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006), which correlates with social and communication impairments. Resting cerebral blood flow near the STS, as assessed with positron emission tomography (PET), also appears to be compromised in ASD. For example, children with ASD display decreased blood flow in several temporal areas relative to children with nonautistic mental retardation, often with correlations between blood flow and scores of symptom patterns (Gendry Meresse et al., 2005; Ohnishi et al., 2000; Zilbovicius et al., 2000).

Functional imaging during social processing tasks confirms atypical neural activity in the STS. Gervais et al. (2004) presented vocal and non-vocal sounds to adults with and without ASD. Among those without ASD, vocal sounds elicited significantly greater BOLD activation along the upper bank of the STS bilaterally than did non-vocal sounds. In contrast, among adults with ASD, activation was approximately equivalent regardless of stimulus type, with very little STS activation observed in any condition. Direct comparisons revealed that the control group had greater activation along the STS during vocal stimuli but not during non-vocal stimuli, and analyses revealed no brain areas in which vocal stimuli elicited greater activation than non-vocal stimuli among the group with ASD. Whereas social stimuli appeared to elicit a unique brain response among healthy adults, this was not the case among adults with ASD. An analogous insensitivity to direction of gaze (direct vs. averted vs. downcast) of photographed faces and to the nature of motion (biological vs. nonbiological) has been shown among children with ASD across event-related potential (ERP) and fMRI tasks, with links between more severe symptoms and less sensitivity as measured physiologically (Carter & Pelphrey, 2006; Pelphrey & Carter, 2008; Pelphrey, Morris, & McCarthy, 2005; Senju, Tojo, Yaguchi, & Hasegawa, 2005).

A final intriguing finding relates to STS activation during a task likely to elicit attributions about others' mental states. Castelli, Frith, Happé, and Frith (2002) presented animations in which geometric shapes appeared to move with either intention (following one another), or with theory of mind ability (coaxing or tricking one another). Compared to control adults, adults with ASD displayed less activation in multiple areas including the STS during presentation of theory of mind animations. Connectivity analyses revealed decreased communication between the STS and the extrastriate region of the occipital cortex, an area of visual cortex that is highly active during observation of theory of mind animations, suggesting that altered connectivity between regions within the larger social brain network might contribute to the neural and behavioral features of ASD (Pelphrey et al., 2005). In particular, Castelli et al. propose that the observed reduction in connectivity between the visual cortex and the STS might reflect a failure of modulation by structures such as the amygdala, which typically enhance sensory processing of socially-relevant information (Adolphs, 2003).

2.2. Fusiform gyrus

A second region critical to social perception is the lateral side of the mid-fusiform gyrus (Kanwisher, McDermott, & Chun, 1997; Kanwisher & Yovel, 2006). Because this region displays a selective response to human faces, it has been referred to as the fusiform face area (FFA; Kanwisher et al., 1997). Although the extent to which the FFA is dedicated to face processing versus fine-grained or expert discrimination of any stimulus class is a matter of debate (see e.g., Diamond & Carey, 1986), the FFA is associated with face detection under a number of different conditions among healthy controls. For example, Kanwisher et al. (1997) found evidence of a double-dissociation between object and face processing, indicating unique and selective regions for each type of event. In addition, the FFA was more responsive to intact faces than scrambled faces or human hands, suggesting that its specificity is not due to low level processing of individual features, nor to all biological stimuli. Furthermore, a recent study demonstrated that among several regions activated by faces (including the FFA, STS, and amygdala), only the right FFA was activated by masked faces, suggesting an automatic response (Morris, Pelphrey, & McCarthy, 2007). Such sensitivity likely facilitates critical social tasks such as recognition of identity and emotional expression of others (Baron-Cohen, 1995; Webb, Dawson, Bernier, & Panagiotides, 2006).

Among individuals with ASD, the FFA is markedly altered, both structurally and functionally. Compared to controls, individuals with ASD display reduced grey matter density, increased grey matter volume, and reduced number of neurons in the FFA, particularly on

the right side (Kwon, Ow, Pedatella, Lotspeich, & Reiss, 2004; Rojas et al., 2006; van Kooten et al., 2008). Diffusion tensor imaging indicates normal size and shape of white matter pathways linking fusiform areas to amygdalar and hippocampal regions, but abnormal microstructure of those same pathways (Conturo et al., 2008).

Many findings indicate group differences in fusiform activation during social perception and cognition. Activation in the FFA is decreased relative to controls during detection of sex or emotional expression of faces, working memory tasks using photographed faces, emotion processing, and judgments of trustworthiness (Koshino et al., 2008; Pelphrey, Morris, McCarthy, & LaBar, 2007; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Pinkham, Hopfinger, Pelphrey, Piven & Penn, 2008). Oftentimes, reduced FFA responding is associated with increased activation in other regions, including those implicated in object processing (Hubl et al., 2003). Such patterns have been interpreted as indicating feature-based processing of faces in those with ASDs (Pierce et al., 2001; Schultz et al., 2000). Some evidence suggests FFA reductions may be mediated by behavioral factors such as diminished gaze fixation, as group differences in activation are less apparent in experimental tasks that draw attention to the eyes (Pelphrey et al., 2007). However, ERP findings examining the N170 component, which reflects very early stage face detection (Dawson, Webb, & McPartland, 2005), suggest that individuals with ASD show FFA deficits above and beyond the effects of diminished attention to the eyes (McPartland, Dawson, Webb, Panagiotides, & Carver, 2004; O'Connor, Hamm, & Kirk, 2005; Webb et al., 2006).

Emerging evidence suggests that the familiarity of faces may moderate fusiform responsivity among individuals with ASD, with familiar faces eliciting more typical responses. Grelotti et al. (2005) described a participant with ASD who displayed no FFA activation to unfamiliar faces, but normal activation to images of familiar animated characters. Similarly, Pierce, Haist, Sedaghat, and Courchesne (2004) found that adults with ASD showed limited activation to strangers' faces, with relatively increased activation to familiar faces. Finally, Pierce and Redcay (2008) found that children with ASD displayed weak fusiform responses to adult strangers' faces, but more typical responses to the faces of familiar adults, familiar children, and unfamiliar children. They suggested that faces that were familiar or depicted children elicited more interest and attention among their participants, consistent with behavioral findings among typically developing children (Bahrick, Netto, & Hernandez-Reif, 1998), resulting in increased recruitment of the FFA relative to unfamiliar adult faces.

In addition to deficits within the FFA, functional connectivity analyses, which describe patterns of correlated activation across neural regions (Friston, 2009), indicate reduced connectivity between fusiform and frontal regions (Koshino et al., 2008), and between the right FFA and the left amygdala, bilateral posterior cingulate, left cuneus, and thalamus while viewing faces (Kleinhans et al., 2008). Kleinhans and colleagues also found that greater symptom severity was associated with poorer connectivity between the right FFA and the left amygdala, but increased connectivity between the right FFA and the right inferior frontal gyrus. Although the connectivity methods used in these studies do not provide information about the directionality of influence (Friston, 2009), it is clear that ASD involves functional alterations in the network of brain regions underlying social cognition, and not only impairments in the FFA itself (Kleinhans et al., 2008). Indeed, computerized training can elicit behavioral improvements in affect recognition in the absence of measurable change in FFA activation, highlighting the interactive nature of the social brain network (Bolte, Hubl, Feineis-Matthews, Dierks, & Poustka, 2006).

2.3. Amygdala

As mentioned above, the amygdala is one of a number of structures thought to modulate incoming sensory information from the FFA and STS, associating emotional and motivational value with stimuli (Adolphs, 2003; Grelotti, Gauthier, & Schultz, 2002). Studies of amygdala functioning point to its involvement in face processing, identification of emotion, perspective taking, social judgments, empathy, and threat detection (Adolphs, 2003; Bachevalier & Loveland, 2006; Grelotti et al., 2002; Schulkin, 2007; Vollm et al., 2006). Damage to the amygdala reduces time spent engaged in direct eye contact during social interactions (Spezio, Huang, Castelli, & Adolphs, 2007), and impairs recognition of both basic (e.g., happiness, anger and fear) and social (e.g., guilt, admiration and flirtatiousness) emotions (Adolphs, Baron-Cohen, & Tranel, 2002). Amygdalar function in such abilities may be developmentally sensitive, as damage sustained early in life impairs reasoning related to theory of mind in humans and social play behavior in animals, whereas damage sustained later in life does not (Daenen, Wolterink, Gerrits, & Van Ree, 2002; Shaw et al., 2004).

Relative to controls, there appear to be differences in both structure and function of the amygdala among individuals with ASD (Schultz, 2005). Studies of afferent white matter pathways to the amygdala indicate reduced connectivity with other brain regions (Barnea-Goraly et al., 2004; Conturo et al., 2008). In addition, volumetric analyses indicate an atypical pattern of amygdala development among those with ASD compared to controls, characterized by excessive early development followed by a regressive loss of neurons later in development, with social deficits corresponding to volume abnormalities (Munson et al., 2006; Schumann & Amaral, 2006; Sparks et al., 2002). In addition, postmortem comparisons reveal reductions in the number of neurons in the amygdala, particularly in the lateral nucleus (Schumann & Amaral, 2006).

Functional studies of the amygdala in ASD have focused largely on activity during face processing. Analyses indicate reduced connectivity between the FFA and the right amygdala, with poorer connectivity predicting clinical severity (Kleinhans et al., 2008). Within the amygdala, activation is reduced during face inversion tasks, implicit emotion discrimination, mental state judgment, and judgments of trustworthiness (Baron-Cohen et al., 1999; Bookheimer, Wang, Scott, Sigman, & Dapretto, 2008; Critchley et al., 2000; Pinkham et al., 2008), although familiarity of faces and the extent to which individuals with ASD attend to the eyes may affect activation, as with the FFA (Dalton et al., 2005; Pierce, Haist, Sedaghat, & Courchesne, 2004). Because the amygdala is critical in assigning emotional significance to stimuli, impairments might indicate insensitivity to the importance of various facial expressions, difficulties assigning motivational value to emotional expressions, and/or impaired ability to use emotional information to guide social behavior (Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Critchley et al., 2000).. This is further supported by evidence of altered affective modulation of the amygdala-mediated startle response following positive and negative stimuli (Wilbarger, McIntosh & Winkielman, 2009).

2.4. Prefrontal cortex

The PFC has traditionally been divided into several subdivisions based largely on anatomical boundaries and functional specificity (Price, 2006). Among these subdivisions is the ventromedial PFC (vmPFC; including the orbitofrontal cortex and the ventral part of the anterior cingulate cortex), which has been implicated in motivation, reward, emotion processing, evaluation of ongoing behavior, and planning for the future. The vmPFC has extensive connections with limbic structures such as the amygdala and hippocampus (Price, 2006). Among typically developing participants, activation in the medial PFC is elicited by tasks prompting empathy, theory of mind, and discrimination of emotional expression (Vollm et al., 2006). Thus, it is of particular relevance to social functioning.

In one of the earliest studies to explore PFC functioning in ASD, Happé and colleagues (1996) found that adults with and without Asperger's disorder showed overlapping but different patterns of

activation within the vmPFC during a theory of mind task. Since then, several additional studies have found reduced or altered patterns of medial PFC activation relative to controls during mental state attribution, irony detection, and processing of emotional facial expressions (Castelli et al., 2002; Gilbert, Meuwese, Towgood, Frith, & Burgess, 2009; Wang, Lee, Sigman, & Dapretto, 2007; Wong, Fung, Chua, & McAlonan, 2008). Furthermore, using single photon emission computed tomography (SPECT), Ohnishi et al. (2000) found diminished resting cerebral blood flow in the medial PFC and anterior cingulate gyrus among children with ASD, with a negative correlation between medial PFC blood flow and social and communicative impairments. Greater activation in the medial PFC predicted higher social competence, consistent with earlier findings of neuropsychological assessments (Dawson, Meltzoff, Osterling, & Rinaldi, 1998).

Within the PFC, there is evidence of anomalies within the anterior cingulate cortex (ACC) in particular. Speculation of ACC involvement in ASD is based on findings indicating that it supports social cognition among controls, including empathy and mental state reflection (Gallagher & Frith, 2003; Vollm et al., 2006). Neuroimaging findings among individuals with ASD indicate reductions in white matter, overall volume, and resting metabolic rates in the ACC (Haznedar et al., 2000; Ke et al., 2008). Moreover, glucose metabolism in the left ACC predicts symptoms related to social interaction and both verbal and nonverbal communication (Haznedar et al., 2000).

To date, very few studies have examined ACC activation during tasks of social cognition or other socially-oriented processes. However, Kennedy and Courchesne (2008) found that adults with ASD had less activation in the ventral ACC than adults without ASD during a social judgment task. Hall, Szechtman and Nahmias (2003) found that adults with ASD displayed greater ACC activation than controls while attempting to match vocal emotions to facial expressions, despite making more errors. The authors suggest such activation might indicate greater task-related attentional demands for participants with ASD, or competition between visual and auditory information. Finally, Henderson et al. (2006) found that a highly verbal subsample of children with high functioning ASD displayed greater error-related negativity (ERN) amplitudes in response to an executive function task than control children, consistent with alterations in the ability to self-monitor ongoing behavior in social settings.

2.5. Mirror neuron system

Somewhat independent of the social brain network is a group of neural regions that are known as the mirror neuron system (MNS). The MNS is thought to include an area of the inferior frontal cortex (IFC; comprised of ventral premotor cortex and the posterior inferior frontal gyrus), and a part of the inferior parietal lobule (IPL; Iacoboni & Dapretto, 2006; Keysers & Fadiga, 2008; Oberman & Ramachandran, 2007).

The MNS is often construed as fundamental to the ability to engage in imitation (Iacoboni & Dapretto, 2006; Oberman & Ramachandran, 2007), in concert with regions such as the superior temporal cortex (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003). The regions of the MNS respond to observation of a range of human actions. For example, the IFC and the IPL are activated when participants move their fingers, yet are activated more strongly when movement is elicited by observation of another person demonstrating the motion (Iacoboni et al., 1999). Similarly, transient lesions to these regions result in selective impairments of imitation (Heiser, Iacoboni, Maeda, Marcus, & Mazziotta, 2003). Recent evidence suggests that the MNS is most active during behavior that is interactive in nature, such as activities in which the observer also participates (Oberman, Pineda, & Ramachandran, 2007). Responsivity of the MNS is especially notable in that the system is sensitive to both observable kinesthetic and unobservable intentional characteristics of actions, and responds during both behavioral and mental imitation. Thus, it likely facilitates social cognitive processes including theory of mind and empathy (Oberman & Ramachandran, 2007).

Structural findings within the MNS suggest cortical thinning relative to controls in the inferior frontal gyrus and IPL, with correlations between thickness and severity of social and communicative symptoms during childhood (Hadjikhani et al., 2006). Moreover, sulcal depth maps reveal shape abnormalities in the inferior frontal gyrus that are more severe among children than adolescents with ASD, consistent with an altered developmental trajectory in this region (Nordahl et al., 2007).

Currently, the primary method of quantifying MNS activity is through the EEG mu rhythm recorded over the sensorimotor cortex, which is highest in amplitude in the absence of active processing, and decreases in amplitude (mu suppression) during observation or performance of goal-oriented actions (Cochin, Barthelemy, Lejeune, Roux, & Martineau, 1998). Studies of mu wave activity among individuals with ASD suggest an absence of this decrease in amplitude. Bernier, Dawson, Webb, and Murias (2007) measured mu suppression while adults with and without ASDs observed, executed, and imitated a variety of actions. Although both groups of participants displayed suppression relative to baseline while executing the actions, those with ASD showed less suppression while observing than controls. Furthermore, less suppression predicted poorer imitation skills, particularly of facial gestures. Similarly, Oberman et al. (2005) found that those with ASD displayed mu suppression to self-performed hand movements, but not to observed hand movements. In contrast, controls showed suppression in both conditions. Familiarity may play a role in mu suppression, as participants with ASD did display significant mu suppression in response to observations of movement by their own hands or those of a parent or sibling (Oberman, Ramachandran, & Pineda, 2008).

Individuals with ASD show MNS impairments during functional imaging tasks as well. During processing of neutral faces, those with ASD display reduced activation in the IFC, and different patterns of functional correlations with other regions relative to controls (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007). Similarly, children with ASD display reduced or absent IFC activation when asked to observe or imitate facial expressions (Dapretto et al., 2006; Nishitani, Avikainen, & Hari, 2004), and the degree of activation correlates with social functioning. In addition, Williams et al. (2006) found that parietal areas of the MNS were less widely activated among participants with ASD during imitation of finger movements, consistent with evidence from studies using TMS during hand and finger movement paradigms (Theoret et al., 2005). Finally, individuals with ASD display reduced functional connectivity between MNS regions and the primary visual cortex (Villalobos, Mizuno, Dahl, Kemmotsu, & Muller, 2005), and longer latencies between sequential activations of the left IPL and left IFC within the imitation circuit (Nishitani et al., 2004).

2.6. Connectivity

In addition to alterations within distinct neural regions, ASD is likely characterized by atypical connectivity between regions important to social cognition and behavior. Theories of altered connectivity have been based both on altered trajectories of brain growth across childhood (Courchesne & Pierce, 2005a) and a long history of findings of impaired global, top-down processing in the context of normal (or even enhanced) local, detail-oriented processing (Courchesne, 2004; Frith, 1989). Courchesne and Pierce (2005b) suggest that ASD may be associated with reductions in long-range connectivity between regions (e.g., frontal and parietal regions), decreasing the likelihood of integrative and multisensory processing, as well as enhanced short-range connectivity, increasing the likelihood of hyperspecialized regions that promote detail-oriented processing strategies (Courchesne, 2004;

O'Connor & Kirk, 2008). Although theories of altered connectivity are not specific to either ASD or social functioning, they are relevant to the present discussion because of their implications for information processing. Given the complex and multisensory nature of social stimuli, under- or over-connectivity in any number of contributing regions would likely impair social functioning (Minshew, Sweeney, & Luna, 2002; Minshew & Williams, 2007; Oberman & Ramachandran, 2008). Indeed, the processing of social stimuli by individuals with ASD does appear to prioritize featural over configural information (see above).

Studies addressing connectivity through investigations of the corpus callosum reveal significant reductions in the volume of the entire corpus callosum and its subregions (relative to overall cerebral volume), as well as alterations in the shape of the midbody region and reduced white matter integrity (Boger-Megiddo et al., 2006; Just, Cherkassky, Keller, Kana & Minshew, 2007; Keller, Kana, & Just, 2007; Vidal et al., 2006). Because the corpus callosum contains fibers that facilitate interhemispheric communication between frontal and parietal areas, structural anomalies in this region could have broad effects on connectivity (Just et al., 2007). Diffusion tensor imaging of white matter pathways has yielded similar results throughout the brain. Relative to controls, those with ASD display abnormalities in white matter integrity and microstructure within the temporal lobe (including the STS), the amygdala, the ACC, the vmPFC, and the frontal lobe in general (Barnea-Goraly et al., 2004; Lee et al., 2007; Sundaram et al., 2008). Of particular interest to social functioning, hippocampo-fusiform and amygdalo-fusiform pathways appear to be atypical, with corresponding effects on face recognition (Conturo et al., 2008). Reductions in white matter integrity, as assessed by DTI, can be due to altered myelination, reduced fiber density, or reduced coherence in the directionality of fiber tracts (Sundaram et al., 2008). However, the precise mechanism(s) involved in ASD are not yet known.

Most relevant to social behavior is functional connectivity during socially-oriented tasks. During face processing, individuals with ASD display a more limited network of activated regions, along with reduced functional connectivity between fusiform, frontal, and amygdalar areas (Kleinhans et al., 2008; Koshino et al., 2008; Welchew et al., 2005). Castelli et al. (2002) reported reduced connectivity between the extrastriate region of the occipital cortex and the STS relative to controls during a task in which participants attributed mental states to animated geometric figures. Using the same task, Kana, Keller, Cherkassky, Minshew and Just (2009) found underconnectivity between frontal regions associated with theory of mind and posterior temporal regions that typically support theory of mind. Moreover, increased social symptom severity corresponds to poorer connectivity between the fusiform face area and the amygdala but greater connectivity between the FFA and inferior frontal gyrus (reflecting greater cognitive demand) (Kleinhans et al., 2008). Thus, observed neural patterns during tasks involving social stimuli appear to have meaningful behavioral correlates. Consistent with fMRI findings, electroencephalographic (EEG) measures of coherence, which assess communication across brain regions, indicate over-connectivity within regions (e.g., frontal lobe) but weak connectivity between regions (e.g., frontal, occipital, and temporal lobes) among those with ASD (Murias, Webb, Greenson, & Dawson, 2006).

3. Trait social affiliation

In contrast to the social brain model, in which a network of regions supports processing of socially-oriented information, are trait models of social behavior, which describe social functioning at the level of personality. Nearly all theories of personality structure posit a construct related to an individual's tendency to engage in and enjoy social relationships, often identified as a higher-order trait of "extraversion" or "reward dependence" (Buss & Plomin, 1984; Cloninger, Svrakic, & Przybeck, 1993; Eysenck & Eysenck, 1975). Depue and Morrone-Strupinsky (2005) describe a trait called affiliation, which reflects the "capacity to experience reward that is elicited by a broad array of affiliative stimuli" (p. 316). Although largely if not fully distinct from constructs such as sociability, social attachment, and separation distress, affiliation is a necessary (but insufficient) component for the establishment and maintenance of social relationships and attachments (Depue & Morrone-Strupinsky, 2005). According to this framework, relationships differ in strength but not in quality, and thus reflect the same set of biological underpinnings.

3.1. Core processes

Depue and Morrone-Strupinsky (2005) posit three core processes through which social affiliation is supported and reinforced: (1) an appetitive phase in which dopaminergically-mediated reward processes facilitate pursuit of biologically-important social behaviors, (2) a consummatory phase in which opioid-mediated reward processes positively reinforce social behavior, and (3) a phase in which affiliative memories facilitate the establishment of long-lasting social bonds. Although discussed here in the context of affiliation, the distinction between appetitive, consummatory, and consolidation phases maps largely onto the model of addiction proposed by Robinson and Berridge (1993), suggesting that some aspects of affiliative processes are common to rewarded behavior more broadly.

During the appetitive phase of affiliation, distal social stimuli such as facial expressions, vocalizations, and gestures serve as unconditioned stimuli, encouraging behavioral approach. Such 'affiliative curiosity' is likely an evolutionary adaptation of mammalian social engagement (Porges, 2001, 2003). This phase relies heavily on the mesolimbic dopamine (DA) system, which originates in the ventral tegmental area (VTA) and projects forward to the nucleus accumbens (NA) in the ventral striatum. The mesolimbic DA system has long been implicated in reward and motivated behaviors, due to its involvement in the rewarding properties of food (Ettenberg & Camp, 1986), sex (Melis & Argiolas, 1995), drugs of abuse (Robinson & Berridge, 1993), and motivation to work for secondary reinforcers such as money (Rolls et al., 1974). Within the VTA and NA, DA release is also associated with a range of affiliative behaviors, including those related to aggression (van Erp & Miczek, 2000), maternal care (Li & Fleming, 2003), and reproduction (Hull, Muschamp, & Sato, 2004). According to Depue and Morrone-Strupinsky (2005), inherently rewarding affiliative stimuli activate the mesolimbic DA circuit, resulting in subjective feelings of desire, wanting, and excitement. In conjunction with the sympathetic nervous system, this supports approach toward a potential mate or social partner.

The consummatory phase of affiliation begins when an individual comes within close proximity to a social partner and a range of intero- and exteroceptive cues evoke social behaviors such as courtship rituals, grooming, mating, or breastfeeding (Depue & Morrone-Strupinsky, 2005). These behaviors increase opioid release and receptor binding in several brain regions, producing subjective feelings of pleasure and physiological calmness. In the immediate context, such a state allows the performance of prosocial behaviors. Over longer periods, the subjective experience of pleasure positively reinforces approach behaviors of the appetitive phase and affiliative behaviors of the consummatory phase, increasing the likelihood that this process will be repeated in the future. These affiliative processes are also facilitated by more instantaneous changes in other systems, such as increased vagal efference, suppressing fight/flight responding (Beauchaine, Gatzke-Kopp, & Mead, 2007), and temporary inhibition of HPA stress responsivity (Porges, 2001). As expected, opioids (particularly the μ-opioid family) are associated with both reward (e.g., Van Ree, Gerrits, & Vanderschuren, 1999) and affiliative behavior across the lifespan (e.g., Guard, Newman, & Roberts, 2002; Kendrick & Keverne, 1989), consistent with their role in this model.

The third phase of the affiliative process promotes the development and maintenance of long-term social bonds (Depue & Morrone-Strupinsky, 2005). During this phase, classical conditioning associates the experience of reward with environmental cues, such as the location, sound, or scent of a partner, which now predict reward. A range of brain structures contribute to this process, including the NA for integration of incentive information, the basolateral amygdala for acquisition of incentive and emotional value, and the OFC for complex stimulus–response–reinforcement associations. As the three phases of the process are repeated, the reward value of a social partner increases, strengthening the social bond (Depue & Morrone-Strupinsky, 2005).

Acting broadly throughout each of these phases are oxytocin and vasopressin, peptides originating in the paraventricular and supraoptic nuclei of the hypothalamus. Oxytocin and vasopressin are similar structurally, and the genes coding for their production are located on the same chromosome (20p13) within close proximity (Caldwell & Young, 2006). During the appetitive phase of affiliation, oxytocin influences incoming sensory information critical to the recognition of a social partner and the development of long-term social bonds (Yu, Kaba, Okutani, Takahashi, & Higuchi, 1996), and interacts with the DA and opioid systems to affect the experience of reward (Numan & Stolzenberg, 2009). During the consummatory phase, oxytocin may facilitate the release of opioids in the brain, increasing the release of β-endorphin (Csiffary, Ruttner, Toth, & Palkovits, 1992). As a result of this cascade of influences, the oxytocin system appears to modulate the formation of affiliative memories that underlie the development and maintenance of affiliative bonds. Consistent with this, it is associated with a vast array of social behaviors in both animals and humans (Guastella, Mitchell, & Dadds, 2008; Pedersen, 2004).

3.2. The appetitive phase in autism

Neurobiologically, disruptions in appetitive responding—regardless of the stimulus type (see above)—may appear as alterations to the mesocorticolimbic DA system (Gatzke-Kopp & Beauchaine, 2007). Relevant findings are quite limited among individuals with ASD. The mesolimbic DA system, which includes the VTA and projections throughout the dorsal and ventral striatum, has been largely ignored to date, with few studies addressing either its structural characteristics or functioning among those with ASD. Indeed, only one functional investigation has examined reward processing in general, and none have examined reward in a social context. Given the potential importance of DA functioning during reward—and during social reward in particular—this paucity of research is unfortunate. Relative to controls, medication-naïve individuals with ASD exhibit increased volume of the caudate nucleus—a part of the dorsal striatum that receives input from the VTA and is rich in DA neurons (Langen, Durston, Staal, Palmen, & van Engeland, 2007). However, NA volumes do not differ between groups, nor are caudate or NA volumes correlated with stereotyped or repetitive behaviors. During a monetary reward task, Schmitz et al. (2008) found increased activation in the left anterior cingulate gyrus and left middle frontal gyrus, areas implicated in motivation and arousal (Bush, Luu, & Posner, 2000). Activation of the left ACC was significantly correlated with scores on the reciprocal social interaction domain of the ADI-R (Lord, Rutter, & LeCouteur, 1994). In addition, children with ASD display reduced DA in medial prefrontal regions as assessed with PET (Ernst, Zametkin, Matochik, Pascualvaca, & Cohen, 1997). Thus, the existing structural and functional evidence, though extremely limited, suggests atypical reward processing among individuals with ASD. Moreover, it suggests specific links between reward processing and social functioning. Assessments of circulating DA more broadly suggest possible elevations of whole-blood DA levels in children with ASD (Herrault et al., 1994), but no consistent differences in the level of HVA, a DA metabolite (Lam, Aman, & Arnold, 2006).

Pharmacologic studies provide only limited insight into the role of DA functioning in ASD. Early arguments for mesolimbic hyperactivity stemmed from the DA antagonistic properties of drugs such as haloperidol and risperidone, which are used to treat aggressive symptoms and behaviors associated with ASD and other psychiatric disorders (Canitano, 2006). In contrast, others have argued for DA hypoactivation. For example, administration of secretin (a peptide hormone) is associated with increases in cerebrospinal HVA levels and improvements in communication and reciprocal social interaction patterns (Toda et al., 2006). As a result, Toda et al. (2006) suggested that secretin increases DA metabolism, consistent with a hypoactivation model. However, despite the appeal of this rationale, the vast majority of placebo-controlled trials indicate that secretin has no appreciable effect on symptoms (Esch & Carr, 2004).

A handful of researchers have also examined DA-related gene expression in ASD. Gadow, Roohi, DeVincent, and Hatchwell (2008) assessed the role of a variable number tandem repeat functional polymorphism in the DA transporter gene (DAT1) among a group of children with ASD. Children homozygous for the 10-repeat allele were more likely to display social anxiety, motor tics, and vocal tics, and less likely to display symptoms of hyperactivity and impulsivity. These findings are somewhat inconsistent with literature on samples without ASD, among whom two copies of the 10-repeat allele has been associated with ADHD (Faraone et al., 2005). Compared with the 9-repeat allele, the 10-repeat results in higher levels of DAT1 production and thus greater synaptic uptake of DA (Fuke et al., 2001). As Gadow and colleagues point out, these findings also appear to conflict with hyperdopaminergic theories of ASD.

The role of polymorphisms in the dopamine D1 receptor gene (DRD1) has also been explored among children with ASD. Using a group of male-only sibling pairs with ASD, Hettinger, Liu, Schwartz, Michaelis, and Holden (2008) identified an overtransmitted haplotype that was associated with increased risk for ASD and stereotyped behaviors, and with impairment in social interaction and nonverbal communication.

A final point relates to the role of DA in early brain development as a possible mechanism for dysfunction later in life. The conversion of DA into norepinephrine is catalyzed by dopamine β-hydroxylase (Kaufman & Friedman, 1965), which is controlled largely by a single gene, DβH (Elston, Namboodiri, & Hames, 1979). Among a sample of multiplex families, Robinson, Schutz, Macciardi, White, and Holden (2001) found that the children of mothers with lower DβH activity were at increased risk of ASD. Concordance rates for DβH alleles did not differ across affected and unaffected siblings, suggesting that increased risk for ASD was unlikely to be due to the direct effects of probands' allelic status. Robinson and colleagues suggest that lower levels of DβH activity result in prenatal conditions that contribute to ASD. Although they could not identify a mechanism, the authors raise the possibility that prenatal exposure to excessive DA levels could cause later down-regulation of DA production or DA sensitivity, with lasting effects throughout development.

3.3. The consummatory phase in autism

Group differences in levels of peripheral β-endorphin, a principle peptide of μ-opioid receptors (Van Ree et al., 1999), are inconsistent across samples, with evidence of both elevations and reductions relative to controls (e.g., Cazzullo et al., 1999; Ernst et al., 1993). Such discrepancies may indicate more subtle alterations in opioid functioning. Indeed, more precise analyses reveal elevations in one form of β-endorphin (C-terminally directed β-endorphin protein immunoreactivity) but decreased or normal levels of a second form of β-endorphin (N-terminally directed; Bouvard et al., 1995; Leboyer et al., 1999). Of note, this pattern of β-endorphin activity may be specific to

individuals with ASD, as it was not found among a group with Rett's syndrome (Leboyer et al., 1994). Discrepancies are also likely due to heterogeneous samples across studies, as β-endorphin levels appear to correlate positively with symptom severity after controlling for IQ (Tordjman et al., 1997).

The issue is further complicated by inconsistent findings regarding treatment with opioid antagonists. Single dose studies of naltrexone, an opioid antagonist, produce minimal behavioral improvement. WillemsenSwinkels, Buitelaar, Weijnen, and van Engeland (1995) found that parent-reported irritability and observed behavioral activity improved following treatment, but no changes were noted in social behaviors. Findings from Cazzullo et al. (1999) indicate that continued administration of naltrexone may be associated with improvement, as twelve weeks of treatment corresponded to significant improvement in symbolic play and behavior problems overall. Bouvard et al. (1995) also reported evidence for improvement following long-term treatment with naltrexone among a subset of their sample.

However, evidence suggests that levels of β-endorphin may be linked with symptom expression, and not with the presence of ASD per se. In addition to correlations with severity (Tordjman et al., 1997), WillemsenSwinkels, Buitelaar, Weijnen, Thijssen, and van Engeland (1996) found that β-endorphin levels were more closely associated with the presence of severe self-injurious behavior than with ASD itself. Across three groups of participants, β-endorphin levels were significantly lower for those with severe self-injurious behavior, whereas levels did not differ according to ASD diagnosis. As the authors discuss, these findings suggest that discrepancies regarding opioid functioning may reflect diverse samples with differing profiles of clinical symptoms. Whereas samples with high levels of severity or self-injurious behavior may display particular patterns of physiological functioning, samples with lower levels of severity may suggest a different set of conclusions.

3.4. Oxytocin and vasopressin in autism

Of all of the affiliative systems reviewed here, evidence for disruption to the oxytocin system in ASD may be the most compelling. Oxytocin, which is generated in the hypothalamus, is released both through the pituitary as a peripheral hormone, and within the brain as a neurotransmitter. Although measures of CSF oxytocin have not been published to date, measures of peripheral oxytocin indicate an elevation in plasma levels among adults with ASDs (Jansen et al., 2006), but a reduction among children (Modahl et al., 1998). Modahl et al. also found that correlations between oxytocin levels and behavioral variables were moderated by an ASD diagnosis. Further analyses with this sample indicated that children with ASD may manufacture oxytocin inefficiently or incompletely. Green et al. (2001) examined absolute and relative levels of OT-X, a prohormone subsequently cleaved to produce oxytocin (Gainer, Lively, & Morris, 1995). Levels of OT-X were significantly elevated among the group with ASD. Moreover, the ratio of OT-X to oxytocin was over twice as high in the group with ASD than in controls. This finding indicates that the control group converted nearly all OT-X into oxytocin whereas the group with ASD did not, suggesting that ASD may be characterized by an incomplete processing of available prohormone (Green et al., 2001). This hypothesis is further supported by Green et al.'s observation that the gene responsible for this conversion (PC2, located at 20p11.1–11.2) is located in close proximity to the oxytocin gene (20p13). Of note, despite its importance in the production of oxytocin, OT-X is functionally distinct and does not activate oxytocin-sensitive sites (Mitchell, Fang, & Wong, 1998). Thus, an over-abundance of OT-X would not remediate a shortage of oxytocin.

Using a double-blind placebo cross-over design, Hollander et al. (2003) examined the effects of oxytocin administration on repetitive behaviors. Compared to their behavior following placebo, adults with ASD displayed fewer repetitive behaviors following intravenous infusion of oxytocin. Oxytocin administration was associated with a reduction in both the amount and number of types of repetitive behavior (e.g., self-injury, ordering, repeating). Moreover, pilot data suggest that oxytocin administered intranasally may induce similar reductions in repetitive behavior, and may reduce cold and/or aloof behaviors and increase performance on tasks of emotion recognition (Bartz & Hollander, 2008). In another study (Hollander et al., 2007), oxytocin administration had positive effects on social cognition during an affect recognition task.

Genetic evidence also supports a role for oxytocin in the expression of ASD. Yrigollen et al. (2008) conducted linkage analyses to explore the role of a number of candidate genes in a group of children with ASD. They found evidence of a link between the ASD phenotype and both the oxytocin gene (OXT, located at 20p13), and the oxytocin receptor gene (OXTR, located at 3p26). Among a group of 195 Chinese Han families, Wu et al. (2005) demonstrated a significant association between ASD and two single nucleotide polymorphisms of the OXTR gene, as well as an overtransmission of two haplotypes containing those polymorphisms. When these polymorphisms were investigated in a sample of Caucasian families, one of the two was associated with ASD (Jacob et al., 2007). The authors attribute this partial replication to a substantial difference in allelic frequencies between the two samples. In an independent sample of children with ASD, Lerer et al. (2008) found evidence for OXTR involvement in ASD, and an association between a particular haplotype, IQ, and the daily living skills scale of the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984).

The gene for the 1a vasopressin receptor (AVPR1a), located on 12q14–q15, has also been explored in relation to ASD. Linkage analyses conducted with 115 families revealed preliminary support for the role of AVPR1a in ASD, yet the significance level was marginal (Kim et al., 2002). Wassink et al. (2004) also found evidence of linkage and linkage disequilibrium in AVPR1a among ASD-affected families. These findings were strongest among families in which the affected member had less language impairment. Moreover, Yirmiya et al. (2006) reported transmission disequilibrium in AVPR1a, in addition to an association between the AVPR1a gene and scores on the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000). Thus, preliminary findings support an association between the 1a subtype of the vasopressin receptor gene and ASD, although the precise nature has yet to be fully clarified.

4. Additional neurotransmitters

Although not central to either of the frameworks discussed thus far, the roles of two additional neurotransmitter systems merit discussion. Both norepinephrine and serotonin contribute to social functioning among typical adults, and have consequently been the focus of investigation among individuals with ASD.

4.1. Norepinephrine

Within the framework of their tridimensional model of personality, Cloninger et al. (1993) describe a trait of reward dependence. Comprised of behaviors such as sentimentality versus insensitivity, social attachment versus detachment, and dependence on social approval versus independence, reward dependence reflects the degree to which an individual's behavior is amenable to the reinforcing effects of social rewards. According to Cloninger's model, reward dependence is subserved primarily by the norepinephrine (NE) system, with an inverse association between NE functioning and social affiliation.

Within the animal literature, links between NE and social behavior are well established. Among vervet monkeys, levels of plasma NE correlate negatively with socially dominant behaviors promoting

affiliation (Dillon, Raleigh, McGuire, Bergin-Pollack, & Yuwiler, 1992). In male rats, NE in the olfactory bulb increases following exposure to potential mating partners, particularly after repeated exposures to the same partner (Dluzen & Ramirez, 1983, 1989). A number of studies indicate that NE modulates the effects of social stimuli on behavior. For example, depletion of NE reduces behavioral responsivity to changes in the social environment (Cornwell-Jones, Decker, Gianulli, Wright, & McGaugh, 1990). Moreover, NE appears to modulate social discrimination and aggression. Whereas depletion of NE impairs recognition of a familiar animal and decreases aggression against intruders, drug-induced elevations of NE improve recognition of a familiar animal (Griffin & Taylor, 1995; Marino, Bourdelat-Parks, Liles, & Weinshenker, 2005). In addition to links between NE and social behavior, findings with animals highlight the sensitivity of the NE system to early experiences such as stress (Liu, Caldji, Sharma, Plotsky, & Meaney, 2000; Morilak et al., 2005). As such, it may be that early experience with social stimuli (or lack thereof) influences NE function later in development, shaping affiliative behavior across the lifespan.

Social behavior and NE are linked in studies of human participants as well. Recent genetic analyses among diverse samples reveal associations between reward dependence and genes related to NE function, such as NE transporter genes and genes important to NE catalysis into epinephrine (e.g., Comings et al., 2000). Moreover, urinary levels of MHPG, an NE metabolite, correlate negatively with scores on measures of reward dependence and positively with aggression (Garvey, Noyes, Cook, & Blum, 1996). The effects of reboxetine, a selective NE reuptake inhibitor, further support a link between NE and social behavior. A single dose of reboxetine is associated with increased cooperation during a social game, and with decreased hand fiddling during a social interaction (Tse & Bond, 2002). Longer term administration results in increased eye contact, social cooperation, and communication (Tse & Bond, 2003). Based upon these findings, Tse and Bond suggest that NE subserves social motivation and drive, particularly with regard to those social behaviors associated with an external focus (e.g., attending to others).

A small body of literature has examined NE functioning among individuals with ASD. Children with ASD exhibit elevated blood plasma levels of NE relative to children without ASD (e.g., Bouvard et al., 1995), consistent with the proposed link between high NE and low reward dependence. However, this conclusion is tempered by inconsistent findings with regard to urinary NE levels among individuals with and without ASD (see Lam, Aman, & Arnold, 2006 for a review). Plasma, urinary, and CSF levels of MHPG (a common but imperfect index of central NE activity; Cooper, Bloom, & Roth, 2003) are also similar across groups, raising doubts that elevated NE underlies the core social impairments of ASD (Minderaa, Anderson, Volkmar, Akkerhuis, & Cohen, 1994; Gillberg & Svennerholm, 1987; Young et al., 1981). Furthermore, although findings of elevations in blood plasma levels of NE have been replicated, Lam and colleagues argue that plasma NE reflects momentary sympathetic arousal (Minderaa et al., 1994) and so may be due to a heightened stress response during the blood draw, and not to broad baseline differences in NE functioning. Thus, the data to date do not offer strong support for alterations in NE function among individuals with ASD.

4.2. Serotonin

In addition to other functions, serotonin is critical to early neural development, regulating the development of serotonergic neurons and neural tissue in regions such as the hippocampus and cerebral cortex (Whitaker-Azmitia, 2001). On the basis of this role, Whitaker-Azmitia advanced the "hyperserotonemia theory" of ASD, in which early exposure to excessive 5-HT leads to a loss of 5-HT terminals, and a consequent decrease in sensitivity to the effects of 5-HT later in development. This theory finds some support in animal models of ASD (Whitaker-Azmitia, 2001), as well as in increased rates of ASD among children exposed prenatally to drugs known to affect 5-HT, such as cocaine and alcohol (Davis et al., 1992; Kramer, Azmitia, & Whitaker-Azmitia, 1994; Nanson, 1992). Moreover, limbic regions including the amygdala, which are altered structurally and functionally in ASD, are enervated richly by serotonergic projections (Anderson, 2002). Indeed, animal studies of early 5-HT overexposure reveal a loss of oxytocin-containing cells in the hypothalamus, as well as altered peptide processes in the central nucleus of the amygdala—changes consistent with theories of down-regulation of 5-HT innervation (McNamara, Borella, Bialowas, & Whitaker-Azmitia, 2008).

Elevated platelet 5-HT has been identified repeatedly in those with ASD (e.g., Anderson, 2002; Anderson et al., 1987). In general, samples of those with ASD show elevations of 25% to 50% compared to samples without ASD, with the greatest differences occurring prior to puberty (Anderson, 2002). However, some studies have failed to find group differences in platelet 5-HT (Croonenberghs et al., 2000). These discrepancies are likely due in part to participant characteristics such as age, severity level, IQ, and medication status, as factors such as pubertal status and verbal communication ability correlate with plasma 5-HT levels (Hranilovic et al., 2007). Furthermore, more precise investigations of serotonergic functioning have found evidence of alterations to specific aspects of the 5-HT system, including transport, receptor activity, and proteins regulating 5-HT synthesis and degradation (Croonenberghs et al., 2000; Hranilovic et al., 2009).

Using positron emission tomography (PET), Chugani et al. (1999) found different developmental patterns in 5-HT synthesis capacity across participant groups. Whereas control children showed high synthesis capacity (approximately twice that of adults) until age 5 years and then a decline to adult levels, children with ASD showed a gradual increase in capacity from 2 to 15 years of age, at which point they displayed values 1.5 times that of healthy adults. The same research group found atypical asymmetries in 5-HT synthesis such that half of their sample with ASD showed decreased synthesis in left frontal, temporal, and parietal regions, and the other half showed decreases in right cortical areas (Chandana et al., 2005). Asymmetries in synthesis have also been found in the frontal cortex, thalamus, and dentate nucleus of boys with ASD (Chugani et al., 1997). In addition, 5-HT transporter binding appears to be reduced in the medial frontal cortex, midbrain, and bilateral temporal lobes among those with ASD (Makkonen, Riikonen, Kokki, Airaksinen, & Kuikka, 2008), as well as in the ACC and posterior cingulate cortex, left parietal cortex, and bilateral frontal and superior temporal cortex (Murphy et al., 2006). Consistent with the role of these regions in social cognition and behavior, binding potential is correlated negatively with social impairment.

Concurrent investigations using genetic techniques have yielded preliminary results. Anderson et al. (2009) examined 45 polymorphisms among 10 candidate 5-HT genes in a sample of 403 Caucasian families containing at least one child with ASD. They found modest support for involvement of the 5-HT pathway in general, with the strongest linkage for the receptor gene HTR3A. Findings regarding a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) are inconsistent and somewhat contradictory, with overtransmission of both the short and long alleles implicated in ASD (Huang & Santangelo, 2008; Sutcliffe et al., 2005). Discrepancies may be due to the fact that elevations in platelet 5-HT are not wholly attributable to variants in the transporter gene, implicating other genes in regulating blood levels (Coutinho et al., 2004).

An additional theory suggests that allelic status might moderate phenotypic expression of ASD without affecting liability for the disorder (Devlin et al., 2005), as with other forms of psychopathology (e.g., depression Willeit et al., 2003). Indeed, Brune et al. (2006) found that children and adolescents with ASD who had the short allele (s/s or s/l) showed greater impairment in nonverbal communication, whereas those who had two copies of the long allele had more severe stereotyped, repetitive, and aggressive behaviors. Among very young

children with ASD, the short allele is also associated with increased cerebral cortical grey matter (Wassink et al., 2007). Thus, the short allele of the 5-HTT gene may have particular relevance for social functioning among those with ASD.

A final approach to the study of 5-HT in ASD involves the effects of 5-HT-related medications. However, despite repeated calls for placebo-controlled, double-blind studies of the efficacy and safety of such drugs, very few such studies have been published (Posey, Erickson, Stigler, & McDougle, 2006; West, Waldrop, & Brunssen, 2009). Of the research that is available, the most promising results are for fluoxetine, a selective serotonin reuptake inhibitor (SSRI), particularly among children who possessed the long allele of the 5-HTT gene (Hollander et al., 2005; Sugie et al., 2005). Despite these successes, however, the bulk of the literature suggests that although SSRIs may affect global functioning or behaviors such as aggression that are associated with ASD, there is little evidence of a significant impact on core social symptoms (King et al., 2009).

5. Conclusions and implications

Each of the models discussed in this review represents a system proposed to underlie normative social functioning in the general population, yet each provides insight at a different level of analysis, including genes, neurotransmitters, hormones, and neural organization and functioning. These models fall along a spectrum of specificity regarding the behaviors and functions they facilitate and/or predict. Whereas some attempt to account for precise behaviors that occur in discrete moments, others explain social behavior in broad, characterological terms. The models reviewed here also vary in the degree to which they have been explored and supported among individuals with ASD, particularly with regard to social behavior. Whereas some mechanisms (e.g., opioid levels) lack consistent evidence of involvement, others (e.g., amygdala responsivity) are more clearly implicated in the behavioral features of ASD. Still others (e.g., mesolimbic DA functioning) appear to hold tremendous potential but have not yet been investigated sufficiently. On the basis of the evidence reviewed in this paper, a number of mechanisms and directions emerge as particularly promising for future research, including amygdala and mirror neuron activity at the neural level, and the dopamine and oxytocin systems at the biochemical level.

Perhaps most promising are recent models that integrate biological systems across multiple levels of analysis and behavior. Dawson and Bernier (2007) offer one such model, integrating dopaminergic and oxytocin/vasopressin functioning with brain regions important to social cognition and behavior within a developmental framework. They propose that ASD is characterized by reduced social motivation early in development, which is reflected in reduced social orientation, less time spent looking at or interacting with others, and less attention to social stimuli. Underlying this deficit are alterations to DA systems critical to reward (such that social stimuli are not associated with reward by the basolateral amygdala and are subsequently less salient) and alterations to oxytocin activity, which would typically modulate DA activity in social contexts. Dawson and Bernier suggest that the failure of oxytocin to selectively enhance the reward value of social stimuli results in decreased attention to and preference for social information. Over the course of early development, brain regions (e.g., STS and fusiform gyrus) that would typically become specialized to process social information fail to do so, and are not integrated into a social reward network. Integrative models such as this make specific, testable predictions with regard to developmental outcomes (Dawson, 2008).

5.1. Implications for intervention and prevention

Regardless of the model in question, an important point throughout this discussion relates to the significance of delineating the biological underpinnings of social dysfunction in ASD. Given that current diagnostic approaches and leading intervention options are behavioral in nature, one might wonder why an understanding of ASD at the biological level is relevant. Beyond any benefits that such an understanding might provide to pharmacological approaches to treatment, what incremental value might a biological approach provide?

Perhaps the most appreciable benefits are those related to intervention. Each of the models reviewed in this paper has a number of implications, with regard to both specific treatment approaches and to overarching principles that cut across treatment methods. Within the social brain framework, evidence of deficits within sensory processing regions suggest that approaches targeting basic processing skills may be critical to building a foundation upon which more advanced social cognition and behavior can be built. Face processing, for example, is fundamental to a range of functions, including identity recognition, emotion discrimination, theory of mind, and nonverbal communication. Addressing deficits in this area may improve subsequent abilities in a more naturalistic fashion than approaches that target advanced social skills without addressing underlying deficits. Faja and colleagues (Faja, Aylward, Bernier, & Dawson, 2008) designed such an intervention, in which individuals with ASD were given explicit instruction focused on featural and configural processing of faces. Following a training period, all participants met behavioral criteria for “expertise” in face processing. Ideally, such an intervention might be followed by training targeting increasingly advanced social cognition (e.g., emotion recognition) to remediate deficits in associated brain regions (e.g., amygdala) in a stepwise or sequential fashion that increases in complexity and sophistication.

A second implication of the social brain model relates to the role of familiarity in neural functioning and social behavior. Across multiple regions and networks, neural activation by individuals with ASD approximates typically developing individuals most closely when the social information to be processed is familiar. Within the regions of the mirror neuron system, among others, activation is enhanced when observed actions are performed by a familiar actor or by oneself (Oberman et al., 2008). Because much of learning relies on imitation (Gopnik, Meltzoff, & Kuhl, 1999), treatment strategies that capitalize on this effect by emphasizing familiarity are likely to reinforce appropriate neural responding and to maximize behavioral improvement. Such approaches might include familiar individuals such as parents, siblings, or peers as trainers and models of desired behavior. In some cases, this technique has been introduced for children with ASD (Jones & Schwartz, 2004), and findings reviewed here suggest that it may benefit adults as well. Moving one step further, desired behaviors may be more efficiently taught if individuals are coached through the creation of training materials (e.g., videos and photographs) that depict themselves or a family member engaging in the goal behavior (e.g., Marcus & Wilder, 2009). Similarly, MNS activation is enhanced when stimuli are interactive in nature (Oberman et al., 2007), advocating for strategies that emphasize participation and experiential learning.

Evidence within the trait affiliation model is similarly instructive. Neurobiological mechanisms underlying reward processing are central to this model, and are suggested as a primary source of dysfunction among individuals with ASD by Dawson and Bernier (2007), particularly with regard to the integration of social stimuli into those mechanisms. Historically, many treatment approaches have emphasized the use of reinforcers (e.g., food and toys) to train desired behaviors such as responding to questions or making eye contact, whereas other approaches have emphasized intensive social interaction (Seigel, 2003). Considering findings from the affiliation model, treatment approaches that blend reinforcement principles with intensive social interaction would be most effective at integrating social stimuli within reward mechanisms. Among existing interventions, the Early Start Denver Model is perhaps the closest to

this ideal, and has thus far yielded promising results (Dawson et al., 2010). Pharmacological methods that target this lack of integration through administration of oxytocin may also prove valuable, as evidenced by data from typical adults (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Guastella et al., 2008) and early pilot trials with adults with ASD (Bartz & Hollander, 2008).

Finally, deficits in the systems underlying the affiliative cycle more broadly suggest the need for structured support during social interactions. The ultimate outcome of this cycle is the creation and maintenance of positive social bonds—in essence, the establishment of selective relationships with particular individuals (e.g., particular peers among a variety of classmates). This process relies heavily on positive, rewarding social experiences that occur repeatedly over time. As such, intervention approaches should emphasize intentional, highly positive social interactions in which structure and support are sufficient to ensure rewarding outcomes. In the context of peer relationships, this might take the form of repeated interactions with trained peers. In the context of parent–child relationships, this may take the form of parent training to enhance the positive valence of daily interactions. Psychoeducation regarding positive behavior management strategies and supportive counseling offered to parents may also be helpful in ensuring positive interactions, particularly in light of the increased stress experienced by parents of children with ASD (Estes et al., 2009). In addition to the behavioral effects of these approaches, they may also facilitate activation of the neurobiological systems underlying social bond formation.

In addition to these specific treatment implications, several broader themes emerge from the models reviewed here. First, biological findings highlight the heterogeneity within the ASD spectrum, and may identify subgroups within the diagnosis that respond differently to various intervention approaches. For example, individuals for whom mirror neuron EEG response approaches normal levels during imitation tasks may benefit more from observational learning than individuals for whom EEG response is more atypical. Given dramatic variation in ASD symptom profile, it may be that assessment with psychophysiological methods would allow more efficient selection among various treatment options. Second, developmental effects observed among individuals with ASD suggest that intervention efforts should extend beyond childhood, through adolescence and into adulthood. Although intervention is often focused on childhood, development of the amygdala and processes regulating serotonin synthesis, for example, continue to change throughout adolescence. Such change suggests plasticity and biological amenability to the effects of intervention provided across development. Finally, evidence of impairment across multiple neural and biological systems suggests the need for comprehensive intervention that is generalizable across contexts and integrates skills in a meaningful way. Treatment programs that target isolated skills (e.g., identifying a smiling face on a flashcard) in discrete settings or circumstances may be less effective than those that target integrated social behaviors (e.g., asking questions of a conversational partner) practiced in real-life settings.

5.2. Importance of a neurobiological understanding

Beyond its immediate translational value, what advantages might a neurobiological understanding of the social deficits of ASD provide? At the level of basic research, such knowledge contributes to an etiological conceptualization. In addition, understanding the neurobiology of psychopathology informs predictions of which children are most vulnerable to poor developmental outcomes (Beauchaine et al., 2008) by highlighting group differences that may serve as candidate biomarkers. The identification of endophenotypes, heritable biological markers intermediate to genes and phenotypes, aids in early prevention efforts, as endophenotypes facilitate family-based genetic studies and the characterization of genetic transmission of risk (Beauchaine, 2009).

Ultimately, a thorough understanding of the neurobiological processes underlying social functioning among those with and without ASD promises to enrich efforts at early identification, prevention, and intervention. It is clear from this discussion that current knowledge falls short of this potential, but each of the models discussed here provides insight in its service, as well as exciting avenues for further research into the links between the behavioral and physiological features of ASD. Although gaps exist between much of the physiological research described here and clinical applications, continued basic and translational work will undoubtedly have an important and sizeable impact for individuals with autism and their families.

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