In this review article, we summarize recent progress toward understanding the neural structures and circuitry underlying dysfunctional social cognition in autism. We review selected studies from the growing literature that has used the functional neuroimaging techniques of cognitive neuroscience to map out the neuroanatomical substrates of social cognition in autism. We also draw upon functional neuroimaging studies with neurologically normal individuals and individuals with brain lesions to highlight the insights these studies offer that may help elucidate the search for the neural basis of social cognition deficits in autism. We organize this review around key brain structures that have been implicated in the social cognition deficits in autism: (1) the amygdala, (2) the superior temporal sulcus region, and (3) the fusiform gyrus. We review some of what is known about the contribution of each structure to social cognition and then review autism studies that implicate that particular structure. We conclude with a discussion of several potential future directions in the cognitive neuroscience of social deficits in autism.

Key Words: autism; social perception; social cognition; functional MRI; cognitive neuroscience

**Neuroanatomical Substrates of Social Cognition Dysfunction in Autism**

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A

utism is a severe and pervasive neurodevelopmental disorder whose etiology remains poorly understood. It is defined broadly by the presence and characteristic developmental course of deficits in three domains of functioning: (1) social reciprocity and engagement, (2) communication and language skills, and (3) stereotyped, repetitive behaviors and narrowed interests [DSM-IV; American Psychiatric Association (APA), 1994]. The prevalence of autism is estimated to be approximately 1 to 2 per 1,000 individuals [Fombonne, 1999] and possibly considerably higher with the inclusion of other disorders falling on the “autism spectrum” [Folstein and Rutter, 1977; see Piven, 2001 for a review]. For example, there is evidence for executive dysfunction in parents [Hughes et al., 1997] and siblings [Hughes et al., 1999] of children with autism and social impairments and distinct personality characteristics (e.g., aloofness and rigidity) in parents of affected children [Wolff et al., 1988; Piven et al., 1994; Murphy et al., 2000]. Parents of affected children also exhibit subtle language and communicative differences [Landa et al., 1992; Piven et al., 1997] and more subtle difficulties managing complex social interactions that demand attention or taking into account social context and other people’s intentions. Similarly, stereotyped and repetitive behaviors may range from simple motor stereotypies and a preference for sameness to much more complex and elaborate rituals, accompanied by considerable distress when these rituals are interrupted. Language deficits, while marked in some autistic individuals who lack basic speech abilities, can be mild and limited to the presence of pragmatic language deficits in higher functioning individuals with autism. In addition to the heterogeneity in these three key behavioral domains, there is also considerable variability in general intellect. While the majority of individuals with autism exhibit mental retardation, IQs can vary from the severe and profoundly mentally retarded range to markedly above average.

The heterogeneity in autism and autism spectrum disorders is expanded still further by the concept of the Broad Autism Phenotype, which suggests that the genetic liability for autism might be expressed in individuals who do not meet diagnostic criteria for autism, but who exhibit phenotypic characteristics of psychological functioning that are milder but qualitatively similar to those seen in autism [Folstein and Rutter, 1977; see Piven, 2001 for a review]. For example, there is evidence for executive dysfunction in parents [Hughes et al., 1997] and siblings [Hughes et al., 1999] of children with autism and social impairments and distinct personality characteristics (e.g., aloofness and rigidity) in parents of affected children [Wolff et al., 1988; Piven et al., 1994; Murphy et al., 2000]. Parents of affected children also exhibit subtle language and communicative differences [Landa et al., 1992; Piven et al., 1997] and
experience higher rates of depression and social phobia [Piven and Palmer, 1999].

Based on the high concordance rate for monozygotic twins and a recurrence risk that is greater than the population rate, there is now considerable evidence that autism is a disorder with a significant genetic component to its etiology [Cook et al., 1998; see Bailey et al., 1995 for a review] with heritability estimates of 60–70% [Veenstra-VanderWeele et al., 2003]. The much higher incidence rate in male compared to female children further suggests a genetic component to the etiology of autism. This could be quite indirect (i.e., through interactional effects of gonadal steroids on brain development), but it could also be more direct, vis-à-vis expression of proteins on the sex chromosomes. For instance, Skuse and colleagues [2003] have argued that impaired social cognition in Turner’s syndrome can be traced to genes on the X chromosome (Xp 11.3) and that the effects of these genes on social cognition are mediated through the amygdala, which is enlarged in Turner’s syndrome. However, research also indicates a role for environmental factors, for example, this is suggested already by monozygotic twins who are discordant for autism. Thus, like most behaviorally defined syndromes, autism is very likely to be etiologically heterogeneous [Rutter et al., 1994]. Roughly 10% of individuals with autism have an associated medical condition thought to play a role in susceptibility to the disease. For example, individuals with single gene disorders such as tuberous sclerosis, fragile X syndrome; and Smith-Lemli-Opitz syndrome have high rates of autism [Baker et al., 1998; Bailey et al., 2001; Martin et al., 2001]. In individuals without an obvious associated medical condition (i.e., idiopathic autism), the underlying mechanism is more likely to be the result of multiple interacting genes or oligogenic inheritance [Pickles et al., 1995; Risch et al., 1999]. Disentangling the precise contributions made by genes and by environment in the etiology of autism remains a critical and largely unmet challenge. Despite this etiological heterogeneity, and despite complexity in the phenotype, it is possible that the various factors contributing to the impaired behavior and cognition seen in autism exert their effect through a circumscribed set of neural structures. That is, it might be the case that the simplest and most compact correlate of autism would be found at the neurological or neuropsychological level, rather than at the genetic or the behavioral level.

Advances in techniques for studying brain–behavior relationships have led to an unprecedented and concerted effort in elucidating the neural basis of autism by linking specific social deficits to dysfunction in specific brain structures (i.e., the cognitive neuroscience of social information processing in autism). These include neuropsychological studies of patients with focal lesions, volumetric quantification of brain structures, anatomical pathway tracing, and imaging of regional brain activation.

fMRI is a noninvasive in vivo imaging method that takes advantage of an endogenous contrast property of the brain, blood oxygen level–dependent contrast (BOLD), to localize changes in blood oxygenation—an indirect measure of underlying neural activity. Since fMRI is noninvasive, does not involve ionizing radiation, can be performed repeatedly, and can be employed to scan relatively large samples of individuals, it is an especially appropriate tool to study autism, where large samples are often required to take into account heterogeneity and where longitudinal studies of children are necessary to characterize functional brain development and behavioral change over time.

Neuropsychological “marker tasks” can provide insights into brain function and can implicate specific brain regions through comparisons with patients who have circumscribed brain lesions and/or other neuroimaging techniques [Johnson, 1997]. Together with functional neuroimaging, lesion studies and detailed neuropsychological testing have generated a wealth of knowledge concerning the neural structures that are the most likely candidates for subserving those cognitive processes that are dysfunctional in autism. These are exciting times for basic research because outcomes of these efforts will prove clinically important in helping to identify specific neurophysiological mechanisms involved in core deficits in autism, thus leading to an improved theoretical understanding for developing and evaluating the effectiveness of novel therapeutic interventions. Emerging neuropsychological models of autism based on the above techniques are already beginning to shed light on candidate mechanisms that may be mediating individual differences in both the expression of autistic symptoms and in their responsiveness to treatment. Characterization of the functional brain phenotypes in autism, as observed through fMRI, may also lead to a clarification of the genetic basis of autism. Longitudinal studies of developmental trajectories and individual differences will give us a more accurate and dynamic picture of autism than would studies that focus only on adults. Neuroimaging studies focused on changing brain–behavior relationships in the developing child may also provide clues to candidate genes in autism, as developmentally important genes begin to be linked to particular patterns of functional brain development, gene expression, and brain phenotypes.

In this review, we summarize recent progress toward understanding the neural structures and circuitry underlying dysfunctional social cognition in autism. We review selected studies from the growing literature that have used functional neuroimaging techniques to map out neurofunctional abnormalities in brain regions underlying aspects of social cognition domains in autism. We also draw upon functional neuroimaging studies with neurologically normal individuals and individuals with brain lesions to highlight how these studies—by providing basic knowledge concerning the neural basis of social cognition—can offer insights that may help to elucidate the search for the neural basis of social cognition deficits in autism. We organize this review around key brain structures that have been implicated in the social cognition deficits in autism: (1) the amygdala, extrastriate visual cortices including the (2) superior temporal sulcus region and the (3) fusiform gyrus. We review some of what is known about the contribution of each structure to social cognition and then review autism studies that implicate that particular structure.

In sketching what is known about the role played by specific neural structures in social cognitive processing, we do not want to imply that such processing is localized to a single brain region, nor would we want to suggest that dysfunction in a given cognitive process results from dysfunction in a single structure. We have little doubt that each of the three structures we will review plays a role in some way in the autism phenotype, but it remains very unclear how exactly they participate as components of the entire neural network and how exactly their dysfunction contributes to pathology. To give just one example; the amygdala has been implicated in processing emotional information from faces, something in which at least some people with autism are impaired. Does their impairment therefore arise from pathology in the amygdala? That conclusion is unwarranted: their impairment may arise...
from entirely different structures connected to the amygdala, and it is in fact conceivable that abnormal amygdala function is a consequence of having autism, rather than a cause of it. The structure–function relationships revealed by cognitive neuroscience often give us only correlative evidence. This is not to say that researchers are not up to the task, it is only to say that understanding autism will be a difficult and complex challenge and that approaches from many different disciplines must be integrated if we are to avoid serious pitfalls.

**NEURAL STRUCTURES IMPLICATED IN SOCIAL COGNITION DEFICITS IN AUTISM**

**Amygdala**

“Social cognition” refers to our abilities to recognize, manipulate, and behave with respect to socially relevant information, including the ability to construct representations of relations between the self and others and to use those representations flexibly to guide social behavior [Adolphs, 2001]. Different sub-disciplines emphasize different aspects of this construct. For example, in social psychology, social cognition describes a range of phenomena including reasoning, stereotyping, and related topics [Kunda, 1999]. In neurobiology, Brothers [1990], defines social cognition more narrowly “as the human ability to perceive the intentions and dispositions of others.” Definitions of social cognition commonly link this construct to social behavior and include social perception (the initial stages of evaluating intentions of others by analysis of gaze direction, body movement, and other types of biological motion), theory-of-mind (the ability to make inferences about the mental states of others), and attributional style (the way one tends to explain other people’s behavior).

Brothers [1990] proposed that the amygdala is part of a small group of brain structures (along with the superior temporal sulcus and gyrus and orbitofrontal cortices) that form the neurobiological basis of social cognition (see Fig. 1 for neuroanatomical structures highlighted in this review). The amygdala is a complex structure comprised of at least 13 nuclei located in the anterior medial temporal lobe with extensive connections to many brain regions including the neocortex, hippocampus, brainstem, thalamus, basal forebrain, and caudustrum [Amaral et al., 1982; Amaral and Insausti, 1992]. Animal models have provided some of the clearest data concerning the amygdala’s function in several aspects of behavior. Studies of rats have demonstrated the involvement of the amygdala in fear conditioning [LeDoux, 1996], the acquisition of fear-related responses to a stimulus via its association with a strongly aversive stimulus. Neurons in the monkey amygdala respond both to the basic motivational significance of stimuli [Nishijo et al., 1988] as well as to their complex social significance [Brothers, 1990; Rolls, 1992]. In humans, amygdala neurons have been found to respond to emotionally salient stimuli of various kinds [Oya et al., 2002] including faces [Fried et al., 1997].

Early studies in nonhuman primates indicated that macaques with bilateral lesions to the amygdala and surrounding medial temporal structures are more tame than nonlesioned monkeys and demonstrate abnormal food preferences and sexual behaviors [Brown and Schafer, 1887; Kluver and Bucy, 1938, 1939]. In an effort to develop an animal model of autism, Bachevalier and colleagues conducted a series of studies with neonatal macaques subjected to bilateral medial temporal lobe lesions that included the amygdala [Bachevalier, 1994, 1996; Bachevalier and Mishkin, 1994]. These monkeys exhibited reduced eye contact, avoided social encounters, displayed inexpressive faces, and lacked many normal play behaviors. They also showed locomotor stereotypies and increases in self-directed activities. These behavioral deficits were strikingly reminiscent of many behaviors observed in autism.

Studies by Amaral and colleagues examined adult male rhesus monkeys with precise bilateral ibotenic acid lesions of the amygdala, a method that provides a relatively selective way to lesion cell bodies but not axons that may be passing through the amygdala. The lesioned animals were paired with unlesioned control monkeys during dyadic social interactions [Emery et al., 2001; Prather et al., 2001]. Contrary to initial expectations, the adult amygdala-lesioned monkeys initiated more social approaches and affiliative behaviors than did the control monkeys. The lesioned monkeys also did not exhibit normal fear behavior in response to novel and fear-provoking stimuli (e.g., snakes) and were socially disinhibited such that they did not exhibit the usual period of reluctance when meeting a novel conspecific. These findings led to the proposal that a primary function of the amygdala is evaluating the environment for potential threats or dangers [Emery et al., 2001] (see also [Amaral et al., 2003] for more recent findings from lesioned monkeys and continued theoretical elaboration). Subsequent studies demonstrated that infant macaques, lesioned at 2 weeks of age, showed an absence of fear of normally fear-inducing stimuli [Prather et al., 2001]. However, the developmentally lesioned macaques also showed more screams and fear grimaces during interactions with other macaques. In human [Fried et al., 1997] and nonhuman primates [Leonard et al., 1985; Nakamura et al., 1992; Rolls, 1992], neurons in the amygdala respond differentially to faces, consonant with the broader responses of amygdala neurons that have been recorded in monkeys in response both to the basic motivational significance of stimuli [Nishijo et al., 1988] as well as to their complex social significance [Brothers et al., 1990]. Overall, the available animal studies demonstrate that the amygdala modulates many responses and cognitive processes based on the emotional significance of stimuli. A common theme is the ability to associate stimuli with their emotional/social value.

Behavioral and structural studies in humans have also clearly pointed to the amygdala’s role in social cognition and social behavior. One specific hypothesis of social dysfunction in autism proposes that this is due to pathology in the amygdala (Baron-Cohen), and abnormal amygdala structure has been linked both to autism (Bauman and Kemper) [Schaumann et al., 2004; Sparks et al., 2002] as well as to genetically predisposed abnormal social behavior in diseases such as autism.
Turner’s syndrome [Skuse et al., 2003]. However, the clearest evidence for the amygdala’s role in social cognition in humans comes from lesion and functional imaging studies. For instance, clear social information processing deficits, including impairments in emotion recognition and social judgments, are found in patients with lesions to the amygdala. Such patients show a relatively disproportionate impairment in recognizing the intensity with which facial expressions signal fear [Adolphs et al., 1994] (see Fig. 2c) as well as a lesser impairment also in recognizing the intensity of other negatively valenced emotions including surprise and anger [Adolphs et al., 1999]. Subsequent studies in several additional patients with amygdala lesion confirmed an impaired ability to recognize emotion from faces, despite a normal ability to discriminate faces perceptually. Some of these studies found a disproportionately severe impairment in recognizing fear [Adolphs et al., 1995; Broks et al., 1998; Sprengelmeyer et al., 1999; Anderson and Phelps, 2000], whereas others found evidence for a broader impairment in recognizing multiple emotions of negative valence in the face, including fear, anger, disgust, and sadness [Adolphs, 1999; Schmolck and Squire, 2001].

Bilateral damage to the human amygdala has also been found to impair social judgments of trustworthiness and approachability of people based on their faces [Adolphs et al., 1998]. Such lesion subjects judge people to look more trustworthy and more approachable than do
healthy controls (see Fig. 1a and b). This finding demonstrates that the role of the amygdala in processing stimuli related to potential threat or danger extends to the complex judgments on the basis of which we approach or trust other people. One proposal [Adolphs et al., 1999, 2000] is that the impairments across diverse tasks reflect the amygdala’s role in recognizing signals that indicate potential threat or danger. But the social impairments due to amygdala damage may be broader yet: one patient described a film of animated shapes (normally seen as full of social content) in entirely asocial geometric terms, despite otherwise normal visual perception and intact social knowledge [Heberlein and Adolphs, 2004].

Functional neuroimaging studies have both corroborated and extended these findings and greatly added to our understanding of the amygdala’s function in neurologically normal humans, particularly with regard to emotion recognition [reviewed in Adolphs, 1999]. Two early studies, one using PET [Morris et al., 1996] and the other fMRI [Breiter et al., 1996], found that the amygdala is activated by facial expressions of emotion (especially fear), even though neither study asked subjects to judge the emotion shown in the stimulus. Other imaging studies have shown that the amygdala is activated by facial expression stimuli, even when these stimuli are not consciously perceived. For example, Whalen et al. [1998] found amygdala activation to fearful faces that were presented briefly and backward masked to render their perception subliminal. These studies suggest that the amygdala is engaged in relatively rapid and automatic processing of facial expressions. In fact, requiring subjects to cognitively label facial expression stimuli, rather than to watch them passively, may result in deactivation of the amygdala [Hariri et al., 2000].

Other human neuroimaging studies illustrate the involvement of the amygdala in normal social cognition beyond its role in emotion recognition. For example, in a PET study of adult males, Kawashima et al. [1999] observed that the left amygdala was activated while subjects interpret gaze direction whereas the right amygdala was activated during eye to eye contact. A recent imaging study of subjects’ ratings of trustworthiness elegantly corresponds to the lesion data presented earlier [Winston et al., 2002]. When normal subjects view faces of people that look untrustworthy, activation is found in the superior temporal sulcus, the amygdala, the orbitofrontal cortex, and the insular cortex.

At least three functional neuroimaging studies of individuals with and without autism have explored the role of the amygdala in autism (see Table 1 for capsule summaries). In the first, Baron-Cohen et al. [1999] required participants to infer the mental or emotional state of another person from the expression of the eyes alone. In behavioral studies conducted outside of the scanner environment, high-functioning subjects with autism reliably show deficits on this task [Baron-Cohen et al., 1997]. The superior temporal gyr, the left amygdala, and the insula were activated in neurologically normal subjects performing this “Eyes Task.” Subjects with autism activated frontal components less extensively than did neurologically normal subjects and showed decreased activation in the amygdala. A second fMRI study examined both explicit (conscious) and implicit (nonconscious) processing of facial expressions [Critchley et al., 2000]. While viewing faces, subjects attended to either the emotional expression (explicit task) or the gender (implicit task) of the face. In contrast to controls, during the explicit task, autistic subjects did not activate the fusiform gyrus and during the implicit task they did not activate the left amygdala region. Finally, in an fMRI study of children and adolescents with autism, Wang et al., [2004] reported that autistic subjects failed to show normal modulation of amygdala activation under different task demands (matching versus labeling faces). During facial expression matching, subjects with autism showed significantly less activity than the control group in the fusiform gyrus, but greater activity in the precuneus. During labeling of emotions, no group differences were observed. Activity in the amygdala was modulated by task demands in the control group but not in autistic subjects.

Some of the most tantalizing (albeit indirect) evidence supporting a role for the amygdala in autism comes from comparisons of subjects with autism to subjects with focal lesions to the amygdala on the same neuropsychological marker tasks. For example, Adolphs et al. [2001] administered a battery of neuropsychological tasks previously used in subjects with focal amygdala lesions to a sample of high-functioning autistic subjects. As illustrated in Figs. 2a and b, the high-functioning adults with autism made isolated abnormal social judgments regarding the assessment of trustworthiness and approachability in faces that parallel similar findings from individuals with bilateral amygdala lesions. Both groups exhibited a significant bias toward overattributing the qualities of trustworthiness and approachability to pictures of faces rated by neurologically normal individuals to be somewhat untrustworthy and unapproachable. Similarly, individuals with autism also have difficulty identifying emotional features in posed facial expressions [Adolphs et al., 2001; Pelphrey et al., 2002]. The facial expression recognition deficits are similar to those seen in patients with amygdala lesions; both populations are impaired at judging faces displaying negative affect, especially fear and anger [Adolphs et al., 2001] (see Figs. 2c and d). Klin [2000] has found abnormalities in the ability of individuals with autism to attribute social meaning to ambiguous, moving geometric shapes, as is typically done by nonautistic individuals [Heider and Simmel, 1944]. The narrations provided by the subjects with autism in the Klin study are remarkably similar to those given by patient SM who described a Heider and Simmel film of animated shapes in exclusively asocial contexts.

Table 1. Functional Neuroimaging Studies Implicating the Amygdala in Autism

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimuli</th>
<th>Key Finding*</th>
</tr>
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<tbody>
<tr>
<td>Baron-Cohen et al. [1999]</td>
<td>Inferring mental states from the eyes region</td>
<td>Decreased activity in the amygdala</td>
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<tr>
<td>Critchley et al. [2000]</td>
<td>Implicit and explicit processing of emotional facial expressions</td>
<td>Failed to activate amygdala in the implicit task and the fusiform gyrus in the explicit task</td>
</tr>
<tr>
<td>Wang et al. [2004]</td>
<td>Face labeling versus matching by emotional expression</td>
<td>Amygdala activity not modulated by task demands</td>
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*Summary of key finding is made with reference to the primary reported difference between subjects with autism and those without autism.
extensively in both human and nonhuman primates. As has been found in studies of the amygdala, some of the clearest findings regarding the function of the superior temporal sulcus have come from studies in nonhuman primates. For example, monkeys use gaze as a component of facial expressions, particularly as it relates to signals of dominance and submission. Monkeys can accurately discriminate small shifts in gaze direction, but they suffer significant deficits in this task following surgical removal of cortex within the superior temporal sulcus [Campbell et al., 1990]. Two prosopagnosic patients tested with the same task used with the surgically ablated monkeys also showed deficits [Campbell et al., 1990]. Employing single neuron recordings, Perrett and colleagues [1985, 1989] identified cells in the macaque anterior superior temporal sulcus that selectively respond to cues from head and gaze direction. Overall, single-cell recording studies in monkeys indicate that cells in the superior temporal sulcus respond to gaze (eye and head) direction [Perrett et al., 1990, 1992], head movement [Hasselmo et al., 1989], mouth movements [Mistlin and Perrett, 1990], hand movements [Perrett et al., 1989], and whole body motions [Oram and Perrett, 1996]. Some of these neurons appear to play a role in social attention by signaling the direction of another person’s visual attention and by processing aspects of the context within which actions are observed [Perrett et al., 1990, 1992]. In addition to the large body of findings concerning action perception, a polysensory region has been described in the monkey superior temporal sulcus (“the superior temporal polysensory region”) that integrates audio and visual components of complex socially significant stimuli [Cusick, 1997].

In humans, the superior temporal sulcus region is defined by Allison et al. [2000] to include cortex within superior temporal sulcus, to adjacent cortex on the surface of the superior and middle temporal gyri (near the straight segment of the superior temporal sulcus), and to adjacent cortex on the surface of the angular gyrus (near the ascending limb of the superior temporal sulcus). This region (particularly posterior portions in the right hemisphere) is involved in perceiving biological motion [for reviews see Allison et al., 2000; Decety and Grézes, 1999] including eye movements [Puce et al., 1998; Wicker et al., 1998; Pelphrey et al., 2003a, 2004a]. The STS region is functionally and anatomically distinct from the more posterior and inferior region MT or V5 (MT/V5) that is localized to the occipitotemporal border [Zeki et al., 1991; McCarthy et al., 1995; Pelphrey et al., 2003b]. Also, portions of the superior temporal sulcus region in humans (as in the monkey) are polysensory, responding to audio and visual components of stimuli [Belin and Zatorre, 2000; Calvert et al., 2000; Calvert, 2001; Wright et al., 2003].

In addition to its role in processing biological motion, there is evidence to suggest that, similar to the anterior superior temporal sulcus in the macaque, the posterior superior temporal sulcus in humans is involved in the analysis and interpretation of the intentions of other’s goal-directed movements and actions seen in other people and is sensitive to other aspects of the context within which observed actions are embedded [e.g., Blakemore et al., 2003; Pelphrey et al., 2003a, 2004; in press]. For example, in a recent series of studies, Pelphrey and colleagues have investigated the degree to which eye-gaze–evoked activity in the superior temporal sulcus is modulated by the context of the perceived eye movement, that is, when the gaze shift correctly or incorrectly acquires a visual target, or whether the eye gaze conveys the intention to engage in or withdraw from a social interaction. In one study, a strong effect of context was observed in the right posterior superior temporal sulcus in which observation of gaze shifts away from the target evoked a hemodynamic response with extended duration and greater amplitude compared to gaze shifts toward the target [Pelphrey et al., 2003a]. That study demonstrated that the perceived context or intention of a gaze shift influences activity in the human superior temporal sulcus. Another study demonstrated that the superior temporal sulcus participates in the visual analysis of social information conveyed by gaze shifts in a more overtly social encounter (e.g., a stranger walking toward the subject and passing him or her in a virtual hallway). Subjects viewed an animated figure that walked toward them and shifted his neutral gaze either toward (mutual gaze) or away (averted gaze) from them. Mutual gaze evoked greater activity in the superior temporal sulcus compared to averted gaze [Pelphrey et al., 2004a]. These findings suggest that activity in the superior temporal sulcus evoked during observation of others’ eye movements is exquisitely sensitive to the context within which those actions are embedded (i.e., approach versus withdraw or goal-directed versus non-goal-directed). These and other findings have strengthened the conclusion that the human superior temporal sulcus region is involved in social perception and social cognition in humans via the visual analysis of social information conveyed by gaze direction and other types of biological motion [Allison et al., 2000]. This idea is in line with systems-level frameworks for understanding the processing of visual information, which have proposed that regions of extrastriate cortex including the superior temporal sulcus and superior temporal gyrus are involved in processing changeable and moveable aspects of faces, whereas regions including the fusiform gyrus process static and structural aspects of the face.

Given the findings concerning the superior temporal sulcus region and aspects of social cognition and social perception, it is not surprising that recent functional neuroimaging research has focused on this region in autism (see Table 2). The role of the superior temporal sulcus region in eye gaze processing is of particular interest. Among the most striking social impairments in autism are deficits in joint attention (i.e., coordinating visual attention with others) and in using information concerning eye gaze to understand others’ mental states and intentions [Loveland and Landry; 1986; Mundy et al., 1986; Baron-Cohen, 1995; Dawson et al., 1998; Baron-Cohen et al., 1999; Frith and Frith, 1999; Leekam et al., 1998, 2000]. Behavioral studies have shown that gaze processing deficits in autism are not based in eye gaze discrimination per se, but result from impairment in using eye gaze to understand others’ intentions and mental states [see Baron-Cohen, 1995 for a review]. In essence, individuals with autism perceive changes in eye gaze direction, but they fail to attribute the intentions and mental states conveyed by eye gaze shifts. Linking these behavioral observations with the demonstrated role of the superior temporal sulcus in social perception suggests the hypothesis that, in autism, activity in the superior temporal sulcus region is not sensitive to the context within which eye movements are observed. This lack of sensitivity to context could mediate deficits in processing social signals conveyed by eye gaze (and probably other nonverbal social signals) because the superior temporal sulcus region in autism does not properly serve the function of processing the intentionality or social communicative value of eye gaze shifts. To date, no published study has yet compared activity associated with observation of eye movements that convey different intentions in autism. However,
an elegant PET study conducted by Castelli et al. [2002] offers indirect support for this hypothesis. Participants with and without autism viewed film segments of geometric figures (similar to the films by Heider and Simmel described earlier) moving about in ways that normally evoke varying attributions of intentionality. Behaviorally, the subjects with autism gave fewer and less accurate descriptions of animations that typically evoked attributions of mental states and intentions. These behavioral findings are in line with Klin’s previous findings using similar stimuli [Klin, 2000]. Relative to controls, subjects with autism demonstrated hypoactivation of the right posterior superior temporal sulcus region in individuals with autism. There was also reduced functional connectivity (i.e., correlation between the time courses from two regions of activation) between the posterior superior temporal sulcus region and a portion of extrastriate visual cortex localized to the inferior occipital gyrus in the autistic subjects.

This PET study also raised the important question of whether the neurobiological basis of the lack of differential superior temporal sulcus activity resides in the cortex of the superior temporal sulcus region itself or whether the dysfunction is the result of failures in communication between the superior temporal sulcus region and other brain structures involved in social processing. Consistent with the possibility of a primary pathology in the superior temporal sulcus region, a PET study of speech perception reported abnormal laterality of responses and hypoactivation of the left superior temporal gyrus [Boddaert et al., 2003] and an fMRI study observed hypoactivation in the superior temporal region to human voices [Gervais et al., 2004]. Also, bilateral hypoperfusion of temporal lobe areas has been observed in children with autism at rest [Ohnishi et al., 2000; Zilbovicius et al., 2000]. Finally, a recent anatomical study comparing cortical sulcal maps in individuals with and without autism found anterior and superior displacements of the superior temporal sulcus [Levitt et al., 2003] and Boddaert et al. [2004] recently reported abnormal superior temporal sulcus volume in autism.

Building upon research to examine polysensory areas of the superior temporal sulcus region in neurologically normal adults [Wright et al., 2003], the role of the superior temporal sulcus region in audiovisual speech perception was recently explored in a small group of high-functioning individuals with autism and neurologically normal controls by comparing responses to various auditory and visual speech stimuli [Collins and Pelphrey, unpublished thesis data]. Four types of stimuli were used to present the auditory and visual components of speech in isolation and in combination: (1) auditory speech alone, (2) visual speech alone, (3) matched audiovisual speech (i.e., the observed mouth movement matched the heard word), and (4) mismatched audiovisual speech (i.e., the observed and heard words did not match). Consistent with a prior report [Wright et al., 2003], the superior temporal sulcus region (see Fig. 3) was activated bilaterally during audiovisual speech perception in both groups of subjects.

For typically developing subjects, hemodynamic responses from this region to the audiovisual match condition were greater than responses to either the auditory or the visual components presented in isolation; the audiovisual mismatch condition evoked a depressed response consistent with the inhibition that is generally observed in paradigms of this type [see Calvert, 2001 for a review]. For the subjects with autism, there was overall hypoactivation in the superior temporal sulcus region and this region responded equally to the matching and mismatching audiovisual stimuli, suggesting a lack of sensitivity to the context (matching or mismatching) of the audiovisual speech stimuli in individuals with autism.

The findings reviewed above are consonant with a potential disruption in the superior temporal sulcus region itself in autism but cannot rule out the alternative hypothesis that there may be abnormal functional connectivity between the superior temporal sulcus region and other regions critical to social understanding. Under this hypothesis, the superior temporal sulcus region is critical for forming a perceptual representation of socially relevant information regarding the actions of others and activates initially in an obligatory manner when the subject perceives an action (e.g., an eye movement or hand gesture) made by another individual. The representation formed in this region is then fed forward to higher systems that analyze the goal-directed and intentional components of these motions. These higher systems may engage and maintain activation in the superior temporal sulcus region via feedback when additional processing is required (e.g., when an action violates the viewer’s expectations) and thus contribute to the activation patterns of the superior temporal sulcus region. The locations of these putative higher systems within this model are unspecified but may include prefrontal regions and/or the amygdala. In individuals with autism, the connection between higher-level systems and the superior temporal sulcus region may be broken, and thus the higher level systems do not engage and maintain activation in the superior temporal sulcus region. In light of this hypothesis, it is interesting to note that a recent fMRI study by Just et al. [2004] found lower functional connectivity between Wernicke’s and Broca’s areas during language processing in subjects with autism, thereby demonstrating the potential value of examining functional connectivity in future studies of the superior temporal sulcus region and social cognition in autism.

Table 2. Functional Neuroimaging Studies Implicating the Superior Temporal Sulcus Region in Autism

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<th>Study</th>
<th>Stimuli</th>
<th>Key Finding</th>
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<tr>
<td>Castelli et al. [2002]</td>
<td>Viewing animations of geometric shapes that elicit varying mental state attributions</td>
<td>Reduced activity in the right superior temporal sulcus and reduced functional connectivity between the superior temporal sulcus and visual cortex</td>
</tr>
<tr>
<td>Boddaert et al. [2003]</td>
<td>Listening to human vocal sounds</td>
<td>Reversed hemispheric dominance and hypoactivation of left temporal regions for perception of speech</td>
</tr>
<tr>
<td>Gervais et al. [2004]</td>
<td>Listening to human vocal sounds</td>
<td>Reduced activity in the left and right superior temporal sulci and gyri</td>
</tr>
</tbody>
</table>

*Summary of key finding is made with reference to the primary reported difference between subjects with autism and those without autism.*
Tended [Gauthier et al., 2000, 2003]. This region, unlike the superior temporal sulcus, may be disproportionately important for processing the static features of faces (e.g., those required to recognize identity as opposed to emotional expression or eye gaze) [McCarthy; 1999b]. Fig. 4 illustrates face-related activity in the right fusiform gyrus in a 9-year-old neurologically normal child. During fMRI scanning, this child observed faces presented periodically within a changing montage of common objects (e.g., kitchen utensils and hand tools). Bilateral activation of the fusiform gyri by faces (yellow-to-red overlay) is evident, with somewhat more extensive activation obtained in the right fusiform. Activation by faces of right lateral cortex in and near the superior temporal sulcus region is also prominent.

Electrophysiological recordings from electrodes placed directly on the fusiform gyrus in patients requiring brain surgery have further demonstrated that face-specific evoked activity in the fusiform gyrus occurs within 200 ms of face presentation [Allison et al., 1999; McCarthy, 1999a; Puce et al., 1999]. Electrical stimulation of these same sites has frequently led to transient prosopagnosia (inability to recognize faces), strongly implicating the discrete regions of the fusiform gyrus in face processing [Allison et al., 1994; see McCarthy, 1999b for a review].

Behavioral studies have provided considerable support for face processing deficits in autism [e.g., Hobson et al., 1988; Loveland et al., 1997], although the precise nature of these deficits has remained unclear. Thus, the fusiform gyrus became a focus of initial functional neuroimaging studies in autism. Table 3 summarizes four functional neuroimaging studies that have focused on the role of the fusiform gyrus in autism. Schultz et al. [2000] conducted the first fMRI study to focus specifically on the fusiform gyrus’ response to faces in autism. They examined face and subordinate-level object perception in a sample of high-functioning adolescents and adults with autism and Asperger’s syndrome and two carefully matched control groups. They found that subjects with autism spectrum disorders, relative to controls, exhibit less face-evoked activity in the fusiform gyrus and recruit regions normally used for nonface object perception to process faces. Three other fMRI studies have also identified fusiform gyrus hypoactivation in autism [Critchley et al., 2000; Pierce et al., 2001; Hubl et al., 2003]. These findings collectively suggest important neural correlates for face processing deficits in adults with autism spectrum disorders. Schultz et al. [2000] suggested a link between amygdala dysfunction in autism [e.g., Critchley et al., 2000] and the lack of the development of a normal face-specific response in the fusiform gyrus (and associated abnormal face perception) in autism, proposing that an early disruption in the amygdala and its connections to temporal cortices, including the fusiform gyrus and superior temporal sulcus, leads to a relative lack of interest in faces and other socially important stimuli and thus to failure of the development of the normal (activity dependent) specificity of regions within the fusiform gyrus in autism. Longitudinal functional neuroimaging studies of face processing children
with and without autism have not been conducted but will be necessary to explore this hypothesis.

The above interpretation has recently been contended. The debate is spurred in part by findings from eye tracking studies of individuals with autism that suggest that autistic people do not look at faces in the same way as do neurologically normal individuals [Klin et al., 2002; Pelphrey et al., 2002]. For example, Pelphrey et al. [2002] demonstrated that individuals with autism spend less time visually scanning the core features of the face, particularly the eyes. These data are illustrated in Fig. 5. Given these findings, it is possible that the hypoactivation of the fusiform gyrus in response to faces is the result of abnormal scan paths. That is, in the three studies that have not controlled for or recorded subjects’ eye movements, the lack of activation might simply have reflected less visual fixation on and visual attention to the faces and particularly the eyes. Indeed, intracranial recordings of face specific N200 responses from the fusiform gyrus have shown that full faces evoke larger N200 than do isolated eyes [McCarthy et al., 1999], but the N200 response amplitude in face-specific sites decreases progressively in the order of faces, eyes, contours, lips, and noses, suggesting that, of the internal face parts, eyes carry significant weight in driving the fusiform’s response to faces.

A recent fMRI study directly addressed this issue. Hadjikhani and colleagues [2004] examined face and object processing in samples of individuals with and without autism. The study used pictures of faces and objects and placed a fixation point in the center of the stimuli to ensure that participants were looking at and attending to the images in the same way. With this design, individuals with autism activated the fusiform gyrus normally when they viewed faces compared to objects. Similarly, in a study that combined fMRI and eye-tracking, Davidson and Dalton [2003] linked hypoactivation in the fusiform gyrus to inattention to the eye region. Specifically, in subjects with autism and controls, there was a strong positive correlation between the number and length of fixations on the eyes and the magnitude of the response to faces in the fusiform gyrus. In discussing this finding, the authors suggested that it reflects active avoidance of gaze resulting from autonomic hyperreactivity to salient social stimuli. This hyperreactivity to the eyes is thought to result from dysfunction in affective regulation processes subserved by the amygdala and prefrontal cortices [Davidson and Irwin, 1999]. Alternatively, both sets of findings (fusiform gyrus hypoactivity and the correlation between the fusiform gyrus responses and attention to the eyes) could reflect a failure to marshal a social response to the environment, rather than active avoidance of social interaction. In essence, the individuals with autism fail to look at faces naturally because the significance of the face, and particularly the eyes, is not appreciated by these subjects. Both possibilities are worthy of serious future research and both may be true but perhaps for different subgroups of autistic individuals.

**Summary**

We have reviewed a substantial body of evidence from neuroimaging studies of individuals with and without autism that indicates important functional abnormalities in autism in neuroanatomical structures thought to play key roles in different aspects of human social cognition. This review highlighted three structures: the amygdala, the superior temporal sulcus region, and the fusiform gyrus. Studies of typically developing adults leave no doubt that these structures function in parallel and should be thought of as elements of a broader system subserving social cognition. For example, when encountering a socially demanding situation, the amygdala will provide a quick and automatic bias with respect to those aspects of the response that pertain to evaluating the potentially threatening nature of the situation or with respect to allocating processing resources to those stimuli that are potentially important but ambiguous. The fusiform gyrus will be engaged to the extent that a perceptual representation of a face needs to be made available, perhaps to make a determination of personal identity. Sectors of the superior temporal sulcus will be called upon to conduct a visual analysis of socially and communicatively important human actions, including movements of facial features and shifts in eye gaze, while other sectors will serve to incorporate auditory and visual components of socially meaningful stimuli, particularly human speech. The rapid integration of the functions performed by each structure would be important to guide social behavior in a typical situation in real life. To date, disruption in each of the components has been studied in autism, but their integration has typically been neglected, and probably for good reason; the initial stages of scientific analysis often demand a focus on the trees rather than the forest. Future goals will be to provide a more detailed account of the relative contributions that each neuroanatomical structure makes to social cognition dysfunction in autism and at the same time to provide a more integrative picture of how functional disruption in one or more structures in autism might reflect dysfunction of the entire system. A challenge for the future will be to offer a more precise account of the interplay.

**Table 3. Functional Neuroimaging Studies Implicating the Fusiform Gyrus in Autism**

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimuli</th>
<th>Key Finding*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schultz et al. [2000]</td>
<td>Face versus object discrimination</td>
<td>Greater inferior temporal gyri and decreased right fusiform gyrus activation during face processing</td>
</tr>
<tr>
<td>Critchley et al. [2000]</td>
<td>Implicit and explicit processing of emotional facial expressions</td>
<td>Failed to activate amygdala in the implicit task and the fusiform gyrus in the explicit task</td>
</tr>
<tr>
<td>Pierce et al. [2001]</td>
<td>Viewing faces and objects</td>
<td>Reduced activity bilaterally in the fusiform gyrus, increased activity in idiosyncratic regions (e.g., frontal, occipital cortex, anterior fusiform gyrus)</td>
</tr>
<tr>
<td>Hubl et al. [2003]</td>
<td>Viewing faces and complex patterns</td>
<td>Reduced activity in the fusiform gyrus during face processing and greater activity in the medial occipital gyrus</td>
</tr>
<tr>
<td>Hadjikhani et al. [2004]</td>
<td>Viewing faces and objects</td>
<td>Identified normal activity levels in the fusiform gyrus after controlling for fixation point</td>
</tr>
</tbody>
</table>

*Summary of key finding is made with reference to the primary reported difference between subjects with autism and those without autism.
between all of these different processes as a function of the detailed specification of the performance demands required by a given experimental task or by a given situation in real life.

**FUTURE DIRECTIONS**

Future directions in research on the neuroanatomical substrates of social cognition dysfunction in autism will clearly build upon the findings to date, extend them to broader issues, and attempt to resolve some of the current discrepancies and debates. Of special value will be attempts to extend the current findings, almost all of which come from studies of adults, to studies of children that incorporate a developmental perspective (i.e., a perspective involving early and longitudinal study of brain and behavioral development). There are several reasons why a developmental perspective on social cognition in autism is compelling and important.

First, deficits in aspects of social cognition may originate from primary impairments in joint attention and imitation, language functioning, and/or the ability to disengage and shift attention. Similarly, given the dynamic and reciprocal relationships between early brain insults and behavioral and cognitive development, autistic symptoms are at best indirect reflections of key neurodevelopmental disturbances. Rather than being a disorder of a specific neuroanatomical structure or circuit, it may be that autism arises from subtle and more diffuse early neuropathology that ultimately affects multiple neural systems, both directly and through compensatory experience-dependent reorganization.

Second, as a neurodevelopmental disorder, autism is a member of a subset of behavioral and cognitive disorders that are linked directly to a primary underlying neurobiological process, that have their onset in the earliest years of childhood, and that have symptoms that change over ontogeny. Although the core deficits in autism persist throughout the lifespan, their actual expression differs depending on the age of the individual. Neuroimaging studies of autism that take into account these psychological and behavioral continuities and discontinuities from childhood to adulthood would better inform us of the neurobiological mechanisms in autism than would studies that provide only a static picture in adults.

Third, very little is known about the neural correlates of social cognition in children or about the changes in brain function that underlie normative development in this domain. Thus, fundamental scientific questions concerning the maturation of the brain and its relationship to changes in social cognition in healthy children remain unanswered. This paucity of information is particularly unfortunate because this basic knowledge is essential to efforts aimed at understanding the neural basis of social cognition deficits in autism. Future longitudinal fMRI studies will allow the field to construct normal developmental curves for the functioning of circuits supporting social cognition by age and sex of the child and reveal changes in the circuitry underlying developments in the selected aspects of social cognition during critical
periods of childhood before, during, and after major developmental epochs. The availability of this normative data will facilitate efforts to characterize atypical developmental pathways in autism.

Fourth, the early diagnosis of autism is an inexact science. Autism is a behavioral syndrome; thus, in contrast to some other neurodevelopmental disorders (e.g., fragile X) no genetic test is available to assist a physician in unambiguously diagnosing autism. Functional brain correlates of autism in children may prove useful in the early identification of autism. To the extent that the proposed research can elucidate developmental trajectories of the neural circuitry supporting pivotal social cognitive skill, it can inform the design of more effective programs for the treatment of autism. By starting early, treatments could target developmental pathways of key neural circuits, perhaps shifting them from abnormal to normal pathways.

Fifth, a developmental perspective can be a useful tool for unraveling the interaction between seemingly disparate levels of organization, such as that from the molecular biology of gene expression to the development of cognitive abilities. The human adult brain and the cognitive architecture it sustains are composed of a complex series of hierarchical and parallel systems that has proven very difficult to analyze in an exclusively top-down fashion. For example, lesions are unlikely to cleanly dissociate different levels of organization or different processes and applying the mapping between brain regions and functions found in normal adults to understanding developmental disorders will be only partially informative. A developmental approach can allow independent observation of different levels of hierarchical control, through observation of how various neuropsychological systems emerge and integrate over ontogeny.

Finally, by defining functional brain phenotypes based on neurofunctional/behavioral developmental pathways, fMRI studies of children with autism have the potential to dissect the heterogeneity present in autism as a behaviorally defined syndrome. Functional neuroimaging studies of autistic children could reveal different brain phenotypes in the circuitry involved in social cognition. These phenotypes might relate to behavioral outcomes and could suggest novel and more targeted intervention and treatment strategies. Early and longitudinal study will be critical in defining brain phenotypes in autism because the shape of developmental trajectories of brain functioning in specific circuits will provide more detail on the nature of the abnormalities in autism than will analysis of brain phenotypes in adults. Brain–behavior studies, particularly those focused on changing brain–behavior relationships in the developing brain, may also provide clues to candidate genes in autism, as developmentally important genes begin to be linked to particular patterns of brain development and gene expression.

Another important avenue for further studies of social cognition dysfunction in autism is the development of stimuli and of tasks with more ecological validity for studying social cognition. Despite the advances reviewed above, progress in the social brain sciences has been slowed somewhat by the lack of ecologically valid social situations that can be manipulated and presented in a socially relevant fashion within the constraint of the testing environments (e.g., a MRI scanner or evoked response potential laboratory). Most studies have imaged subjects during viewing of simple, static images that are confined to a single stimulus category. While this strategy has been fruitful for identifying regions of the brain with functional specificity for particular classes of objects, several questions remain unanswered about the moderating effects of the context of stimulus presentation on these brain regions. For example, a key element for successfully imaging brain regions during social perception is that social interactions may depend upon the "perceived" participation of the individual being tested in the very scene that is depicted. The development of naturalistic social stimuli will allow the field to explore important questions regarding the neural basis of social perception and cognition—questions that have gone largely unanswered because of the impoverished stimulus environment typically used in these studies. Indeed, subtle but important social deficits are often most evident in high-functioning individuals with autism when these individuals are faced with relatively unstructured social settings that demand sensitivity to context and the intentions of others.

As future studies begin to shift focus from functioning in single regions to interactions between brain regions (and their possible disruptions in autism) involved in social cognition, continued developments in techniques for noninvasive imaging of the human brain will remain key. We will see researchers more frequently combining data from complementary imaging techniques for examining structure, function, and connectivity (i.e., multimodal imaging) in the study of social cognition dysfunction in autism. For example, the combined use of diffusion tensor imaging (DTI) and fMRI in studies of individuals with and without autism holds great promise for studying the role of functional connectivity in deficits that characterize autism. DTI is a technique that permits the tracking of white matter fiber tracks by quantifying the diffusion of water molecules in the brain. Molecules diffuse less readily across membranes, and part of the MRI process facilitates the directional mapping of white matter tracts based on this principle. Applying such a technique in autism would help explicate any differences in the trajectories and connections of neural tracts between brain areas.

REFERENCES


