CHAPTER 55

Neural Endophenotypes of Social Behavior in Autism Spectrum Conditions

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Abstract

Autism is characterized by qualitative impairments in social interaction, communication, and stereotyped repetitive behaviors and/or restricted interests. Beyond these diagnostic criteria, autism is viewed as a neurodevelopmental condition with possibly several etiologies that manifest in complex patterns of atypical structural and functional brain development, cognition, and behavior. Despite the multidimensional nature of and substantial variation within the autism spectrum, impairments in social interaction remain among the most visible hallmarks of the condition. It is this profound developmental deficit in the social domain that makes autism a unique case in the field of social neuroscience. This chapter contributes to the dialogue amongst both the fields of autism research and social neuroscience by deliberately taking the stance of asking how we can understand more about the etiological mechanisms underlying social behavior in autism. It presents a multi-level overview of the literature on the behavioral, neural, and genetic underpinnings of social functioning in autism spectrum conditions (ASC). The main objective is to highlight the current state of the field regarding theory of mind/empathy difficulties in ASC, and then to suggest distinct candidate neural endophenotypes that can bridge the gap between social behavior and genetic mechanisms.

Keywords: autism, Asperger syndrome, social cognition, social behavior, theory of mind, mentalizing, empathy, face-processing, meta-analysis, neuroimaging, endophenotype, social development

Autism, as defined by ICD-10 and DSM-IV criteria, is characterized by qualitative impairments in social interaction, communication, and stereotyped repetitive behaviors and/or restricted interests (APA, 1994; ICD-10, 1994). Beyond these diagnostic criteria, autism is viewed as a neurodevelopmental condition with possibly several etiologies (Geschwind & Levitt, 2007) that manifest in complex patterns of atypical structural and functional brain development (Belmonte et al., 2004; Courchesne et al., 2007), cognition, and behavior (Baron-Cohen & Belmonte, 2005; Volkmar, Lord, Bailey, Schultz, & Klin, 2004). Despite the multidimensional nature of and substantial variation within the autism spectrum, impairments in social interaction remain among the most visible hallmarks of the condition. It is this profound developmental deficit in the social domain that makes autism a unique case in the field of social neuroscience. However, autism research also benefits dramatically from progress in social neuroscience, since such progress informs us about the etiological mechanisms and processes underlying the social hallmarks of autism. Thus, both fields are critically locked in a bidirectional

interaction and it is the dialogue amongst researchers in both fields that can help provide further advancements in our knowledge of both fields.

For the purposes of this chapter we contribute to the dialogue amongst both the fields of autism research and social neuroscience by deliberately taking the stance of asking how we can understand more about the etiological mechanisms underlying social behavior in autism. Historically, the most concretely testable and widely documented of the social impairments in autism was the ability to mentalize[1] and/or to rapidly and flexibly manifest empathy with others (Baron-Cohen, 1995; Baron-Cohen, Leslie, & Frith, 1985; Frith, 2001). An increasing body of evidence also relates autistic mentalizing deficits to computationally and developmentally prior abnormalities in social and other perceptual processes (Dawson et al., 2004; Rogers & Pennington, 1991; Schultz, 2005). However, amongst the search for explanations of autism, at the cognitive, neural, and genetic levels, some have argued that there may be no single overarching explanation for all of the phenotypic variability (Happé, Ronald, & Plomin, 2006; Ronald, Happé, Bolton, et al., 2006). Many researchers now tend to view autism as a set of subtypes that fall under the broad label of autism spectrum conditions (ASC). Thus, if we are to identify the underlying etiological mechanisms giving rise to various types of autism, there is a need to characterize individuals in terms of variables closer to these mechanisms.

Recent thinking in the field of psychiatry has led to the concept of intermediate phenotypes ("endophenotypes"; see Box 55.1) which are one step closer to the genetic mechanisms that, in interaction with environmental factors, ultimately give rise to variability within the diagnostic phenotype (Gottesman & Gould, 2003; Meyer-Lindenberg & Weinberger, 2006). For example, in different individuals with ASC, the same abnormality of neural information processing may arise from partially or wholly distinct sets of factors. Although the final common pathway underlying the diagnosis may lie at the level of neural information processing, inter-individual variations in the genetic and environmental factors from which this neural abnormality arises produce corresponding inter-individual variations within and outside the common pathway. In this endophenotypic sense, a fractionable, multiple-factors view of autism is not incompatible with a unified, final common pathway account (Belmonte, Bonneh, et al., 2009).

Box 55.1. Endophenotype

Endophenotypes are defined as "measurable components unseen by the unaided eye along the pathway between disease and distal genotype" (Gottesman & Gould, 2003). Endophenotypes can be of variable depth, in that some measures (e.g., cellular activity as measured by single-unit electrophysiology) might be closer to the genetic end, whilst others such as reaction time in a behavioral task could constitute an endophenotype that is closer to the end marked by clinical diagnosis. Neural endophenotypes (as identified by structural and functional neuroimaging) lie in an intermediate position in this scale measuring the "depth of endophenotype." Meyer-Lindenberg and Weinberger (2006) were among the first to propose a framework for identifying neural endophenotypes for understanding complex psychiatric conditions.

In this chapter we present a multi-level overview of the literature on the behavioral, neural, and genetic underpinnings of social functioning in autism spectrum conditions (ASC). Our main objective is to highlight the current state of the field regarding theory of mind/empathy difficulties in ASC, and then to suggest distinct candidate neural endophenotypes that can bridge the gap between social behavior and genetic mechanisms (see Figure 55.1). We start with a review of behavioral and neuroimaging studies on theory of mind/empathy in ASC. Rather than providing an exhaustive review of all studies in ASC, we give a succinct overview of widely used and consistently replicated behavioral assays or tests of this construct in ASC. While theory of mind/empathy is a broad construct (Baron-Cohen & Wheelwright, 2004; Belmonte, 2008; Blair, 2005; Chakrabarti & Baron-Cohen, 2006; de Vignemont & Singer, 2006; Preston & de Waal, 2002) (see Box 55.2), this review highlights the most pertinent aspects of theory of mind and empathy that have been systematically addressed (see Table 55.1 for an overview).

In addition to the overview of research on theory of mind/empathy, we go one step further and suggest candidate neural endophenotypes for social impairment in ASC. To this end, we discuss results from recent meta-analyses of functional neuroimaging studies relevant to social behavior in people with and without ASC. By providing a quantitative insight into the literature relating to social behavior in autism (e.g., face perception, facial emotions, eye gaze, mentalizing, self-referential cognition), we illustrate how a "candidate neural endophenotype" should focus on the most robust and consistent

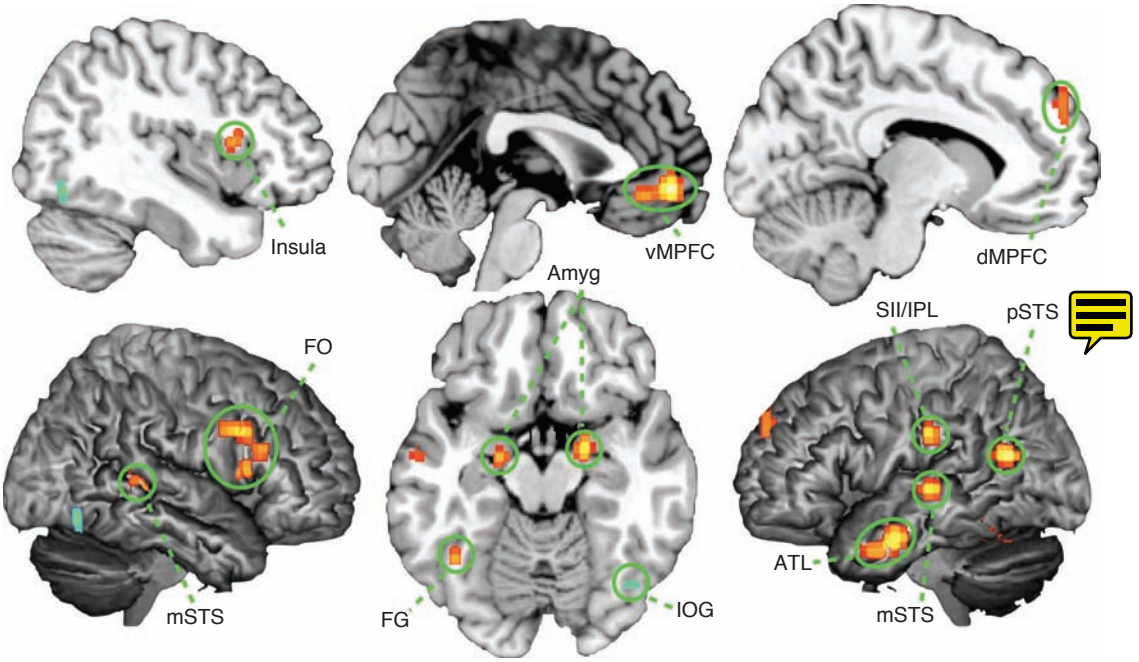

Fig. 55.1 Intermediate phenotypes (endophenotypes) in psychiatry. The far left (left of the solid vertical line) represents the primary structure of DNA, variations in which have been related to clinical phenotypes (far right) in traditional genetic association studies. The vertical line in the right is a dotted one to denote that clinical diagnoses (especially for ASC) exist along a continuum, that there is no strict distinction from the range of observed behavior. A range of intermediate phenotypes (e.g., mRNA/protein abundance and activity, cell population response, overt/covert behavior) exists between these two ends, which are all potential endophenotypes. An endophenotype could be closer to the DNA end (in which case effect sizes of genetic association would be higher), or closer to the clinical diagnostic end (which could account for why most genetic studies find multiple associations of low-medium effect size). Thus the "depth of endophenotype' (i.e., how close a particular endophenotype is to the DNA end of this continuum) can help determine the strength of a genetic association. The horizontal arrow at the bottom of the figure is bidirectional, to denote that just as DNA can influence behavior through the set of endophenotypes, the environment can in turn impact on gene expression.

neural systems that differ between groups. We also illustrate how endophenotypes may be refined by highlighting the common and distinct neural systems underlying subdomains of social behavior such as theory of mind and face processing. Finally, we discuss evidence from humans and other animals for genetic contributions to social behavior and autism and suggest directions for future research that will integrate genotypic and endophenotypic levels of analysis.

Theory of Mind in ASC

Inquiry into theory of mind began with the seminal paper by Premack and Woodruff (1978), provocatively

Box 55.2. Theory of Mind, Mentalizing, and Empathy

Theory of mind (ToM) allows us the capacity to infer the full range of mental states (beliefs, desires, goals, intentions, imagination, emotions, etc.) that cause action, in a top-down manner. In brief, having a theory of mind is to be able to reflect on the contents of one's own and other's minds (Baron-Cohen, 1995). *Mentalizing* is a synonymous term to theory of mind. *Empathy* is a superordinate category, encompassing ToM as well as automatic components of emotion perception and the ability to respond to others' emotions in an appropriate way. Empathizing is defined as the ability to identify emotions, thoughts, and other mental states in others, and to respond to these in an emotionally appropriate way (Baron-Cohen & Wheelwright, 2004). Empathy consists of three main fractions, including a) cognitive empathy (identical to ToM), b) affective empathy, which is responsible for our automatic reactions to others' emotions, and c) sympathy/prosocial Behavior, which is involved in making an emotionally appropriate motor response (for a discussion, see Chakrabarti & Baron-Cohen, 2006). For the purposes of the meta-analysis reported in the *Neural Systems Involved in ASC Social Impairment* section, we have taken a broad approach, including all studies that tap the broad construct encompassing theory of mind, and empathy, either directly or indirectly.

Table 55.1 Overview of the Common Behavioral Results in the Domains of Theory of Mind/Empathy in ASC.

	Experimental paradigms	Observed differences	Primary example references
	Vocalizations		Hobson (1986)
	Body Posture	ASC<Controls	Hobson (1986)
Emotion Recognition			
	Facial Expression	ASC<Controls (accuracy)	Humphreys et al. (2007)
		ASC>Controls (reaction time)	Humphreys et al. (2007)
	Reading the Mind in the Eyes task	ASC<Controls	Baron-Cohen et al. (2001a)
	False Belief Task	ASC< Controls	Baron-Cohen et al. (1985)
			Happé (1995)
Theory of Mind	Strange Stories Task	ASC<Controls	Happé (1994)
			Happé et al. (1996)
	Faux pas test	ASC<Controls	Baron-Cohen et al. (1999)
	Animations Task	ASC<Controls	Klin (2000)
			Abell et al. (2000)
	Unexpected Contents Task		
	Smarties Task		Perner et al. (1989)
			Leslie & Thaiss (1992)
	Plasters Task		Williams & Happé (2009)
	Appearance-Reality Distinction		Baron-Cohen (1989)
	Self-Reference Effect in Memory		
	Self>Semantic	ASC<Controls	Toichi et al. (2002)
	Self>Dissimilar Non-Close Other	ASC<Controls	Lombardo et al. (2007)

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Table 55.1 Continued

	Experimental paradigms		Observed differences	Primary example references
			ASC<Controls	Henderson et al. (2009)
Self		Self>Similar Close Other	ASC=Controls	Lombardo et al. (2007)
	Self-Knowledge Estimation			
		Self>Close Other	ASC<Controls	Mitchell & O'Keefe (2008)
	Alexithymia		ASC>Controls	Hill et al. (2004)
				Lombardo et al. (2007)
	Self-Conscious Emotion			
		Experience	ASC<Controls	Hobson et al. (2006)
		Recognition	ASC<Controls	Heerey et al. (2003)
				Hobson et al. (2006)

Tasks have been broadly classified into categories marked by single colors. RMET in particular has been marked in a special category, as it represents an overlap of ToM and emotion-recognition paradigms.

titled "Does the chimpanzee have a theory of mind?" We first tested theory of mind ability in ASC via a modified version of Wimmer and Perner's (1983) False Belief test. In this test children are presented a brief story involving two dolls, Sally and Ann. Sally enters a room and puts her marble into her basket and then leaves the room. Whilst she is away, "naughty" Ann takes Sally's marble out of the basket and puts it into her own box. Upon Sally's return the crucial test question to children was "Where will Sally look for her marble?" Whilst 85% of typically developing children were able to attribute a false belief to Sally (e.g., "Sally will look in her basket"), 80% of children with autism failed to attribute a false belief to Sally (Baron-Cohen et al., 1985). Various manipulations and control tasks have been tested and all point to a similar conclusion, that children with autism have a marked deficit in attributing beliefs to others. In a meta-analysis Happé (1995) clarified that some children with ASC do eventually acquire the ability to pass this false belief test, but only after a delay of approximately 5 years relative to typically developing children.

However, even where individuals with ASC pass traditional false belief tests, significant social disability persists, reflecting that more subtle deficits in mental state attribution exist than are measured by the standard false belief test. Traditional false belief tests yield only two outcomes: pass or fail. As the Happé (1995) meta-analysis highlighted, this limitation of a relatively simple measure of theory of mind spurred the development of more complex tests that yield greater variability. In one such test, the Strange Stories Test (Happé, 1994), participants read vignettes about everyday situations where the characters say things that aren't meant literally. Comprehension on this test requires the attribution of more complex mental states and intentions such as deception, joking, pretence, persuasion, and sarcasm. Even more able individuals with ASC who pass both first- and second-order false belief tests are impaired at giving context-appropriate mental-state explanations for characters' nonliteral utterances.

The Strange Stories paradigm was employed in one of the first neuroimaging studies on theory of mind in autism (Happé et al., 1996). Individuals with

autism show hypoactivation of the dorsomedial prefrontal cortex (dMPFC) during this task. Later fMRI studies by Wang and colleagues probed similar aspects of pragmatics in language that intersect with mentalizing ability (Wang, Lee, Sigman, & Dapretto, 2006, 2007). These studies also showed that people with ASC hypoactivate dMPFC. However, when individuals with ASC are explicitly directed to attend to social cues such as facial expression or prosody, dMPFC activation is restored to a level similar to controls' (Wang et al., 2007). This set of results highlights the role of attention to social cognitive cues in engaging intact abilities, and suggests that in many cases, skills that are assumed to be absent in autism may simply not be rapidly and flexibly activated by social cues.

As the research of Wang and colleagues demonstrates, perceptual social cues are integral for more advanced theory of mind ability. We developed an advanced theory of mind task that relies more on perceptual rather than linguistic cues. During the Reading the Mind in the Eyes task (RMET) (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001a) participants are shown photos of just the eye regions of faces. Individuals are asked to judge what the person in the picture is thinking or feeling, based solely on viewing the eyes. These judgments involve complex emotion recognition and show a fairly normal distribution within the general population. This point is important because for most theory of mind tests which people with autism do not pass, typically developing control participants pass at ceiling rates. On the RMET, even the most able individuals with ASC, such as adults with Asperger syndrome, show impaired performance, suggesting that theory of mind deficits are a core characteristic of all individuals on the autistic spectrum. The RMET has also demonstrated sensitivity in detecting familial effects, as both parents and siblings of individuals with ASC perform significantly worse when compared to parents and siblings of control children (Baron-Cohen & Hammer, 1997; Dorris, Espie, Knott, & Salt, 2004; Losh & Piven, 2007; Losh et al., 2009). This concurs well with other recent demonstrations of familiality of face-processing deficits in ASC (Adolphs, Spezio, Parlier, & Piven, 2008; Losh et al., 2009).

Using fMRI we probed the neural correlates of performance on the RMET and found hypoactivation in ASC within structures important for emotion and action/perception mirroring: the frontal operculum (FO), amygdala, and insula (Baron-Cohen et al., 1999). These results differed from the earlier studies revealing dMPFC involvement in pragmatic language aspects of theory of mind in autism and highlight the possibility of dissociable neural mechanisms for theory of mind tasks that involve perceptual versus linguistic cues.

A significant drawback of many tests of theory of mind has been their reliance on verbal ability and/or an explicit focus on mental state attribution. As noted early in the study by Wang and colleagues (2007), mentalizing activation in ASC was below normal when the individual was left to process the task in whatever way was natural for them, but could be normalized by explicitly directing attention to social cues. Thus, there is a need for measures to test whether the mentalizing abnormalities that persist throughout life are indicative of an underlying deficit in spontaneously mentalizing. One such nonverbal measure of automatic mental state attribution (i.e., *implicit* mentalizing) without an explicit focus on mental states is the Social Attribution (or Animations) Test. In the Animations test, an individual watches an animation of two geometric shapes moving about on a computer screen. In one set of animations, the shapes move in such a sequence that most typically developing individuals will spontaneously anthropomorphize into a narrative full of mental state references. People with ASC, including those who demonstrate first- and second-order false belief ability, are less prone to attribute cognitive and affective mental states to these animations spontaneously. When people with autism do attribute mental states, they are often contextually inappropriate (Abell, Happé, & Frith, 2000; Klin, 2000). Similar to the study by Wang and colleagues, this paradigm demonstrates an absence of automatic attribution of mental states in the absence of explicit instructions to do so. The two fMRI studies to date employing the Animations task have shown hypoactivation of mentalizing areas such as the dMPFC and posterior superior temporal sulcus (pSTS) (Castelli, Frith, Happé, & Frith, 2002; Kana, Keller, Cherkassky, Minshew, & Just, 2009).

Convergent recent evidence further extends the notion that individuals with autism do not spontaneously engage with the mental worlds of others. In our own recent work (Barnes, Lombardo, Wheelwright, & Baron-Cohen, 2009), we wanted to see whether adults with ASC would be able spontaneously to extract rich mentalistic information from naturalistic film clips depicting moral dilemmas and to convey them through written narratives. While control participants wrote narratives full of mental state references, adults with autism produced

significantly shorter and more constrained narratives that focused less on mental states. This example corroborates the results from the Animations test: Adults with autism do not spontaneously mentalize in situations that approximate naturalistic settings.

Senju, Southgate, White, and Frith (2009) demonstrated a similar phenomenon through dependent measures that are completely nonverbal. In this study, participants watched a scenario where a puppet hides a ball in one of two boxes in front of an observant other person. The other person then turns away briefly, and the puppet removes the ball from the box. Upon the test trial phase, a light flashes, indicating to the participant that the person will reach for the box in which they believe the ball is hidden. Using an eye-tracker, the researchers were able to measure anticipatory looks to the box with which participants should have associated the observer's false belief. Adults with Asperger syndrome who could pass the standard Sally-Ann false belief test showed no anticipatory gaze fixations to the false-belief location. This ability emerges as early as 2 years of age in non-ASC children (Southgate, Senju, & Csibra, 2007), yet is absent in adults with Asperger syndrome.

The Self and its Link to the Social World in Autism

The historical focus in autism research on mentalizing deficits as they relate to *other* people is complemented by more recent studies of how people with autism understand their *own* mental states. Behavioral studies suggest that people with autism are as impaired, if not more so, in explicit awareness of their own mental (Baron-Cohen, 1989; Leslie & Thaiss, 1992; Perner, Frith, Leslie, & Leekam, 1989; Williams & Happé, 2009) and other aspects of self-referential cognition (Hill, Berthoz, & Frith, 2004; Lombardo, Barnes, Wheelwright, & Baron-Cohen, 2007; Toichi et al., 2002). See Table 55.1. Theoretical accounts have proposed that people with autism are locked in an egocentric stance (Baron-Cohen, 1995; Frith & de Vignemont, 2005) and that deficits in self-processing are integrally linked to how individuals with autism relate to the social world (Baron-Cohen, 2005; Frith, 2003; Frith & Happé, 1999; Happé, 2003; Hobson, Chidambi, Lee, & Meyer, 2006). In the context of theoretical accounts of social cognition such as simulation theory (Goldman, 2006) and self-other narrative practice (Hutto, 2007), and the abundance of research demonstrating overlapping/shared neural representations for self and other (Keysers et al., 2004; Lombardo, Chakrabarti, Bullmore, Wheelwright et al., 2010; Mitchell, Macrae, & Banaji, 2006; Singer et al., 2004; Wicker et al., 2003), the case of autism presents a unique opportunity to test such theoretical predictions.

To date, five neuroimaging studies have examined self-referential processing in autism. In the domain of self-recognition, Uddin and colleagues (2008) asked participants to make self-recognition judgments about pictures varied continuously in "self" or "other" content. Both participants with and without ASC activated a right-lateralized frontoparietal system for self-recognition judgments. However, people with ASC did not activate this system when making other-recognition judgments. Thus, while this task suggests a deficit for recognizing others, it did not distinguish the two groups in terms of a self-referential impairment and parallels findings suggesting that individuals with autism have no difficulties in self-recognition at the appropriate age (Dawson & McKissick, 1984; Lind & Bowler, 2009).

In the realm of reflective emotional self-awareness, Silani and colleagues (Silani et al., 2008) instructed participants to rate how *they* felt after viewing emotionally charged pictures, in comparison to judging how much color was in the pictures. During emotional self-appraisal, people with autism showed hypoactivation within the dMPFC, posterior cingulate cortex/precuneus (PCC), and temporal pole. This hypoactivation in the dMPFC during emotional self-introspection is in the same area on the paracingulate sulcus where previous studies observed other-referential mentalizing difficulties (Castelli, Frith, Happé, & Frith, 2002; Happé et al., 1996; Kana, Keller, Cherkassky, Minshew, & Just, 2009; Wang et al., 2007).

In the context of reflective trait judgments about self or other, Kennedy and Courchesne (2008a) asked participants to judge the descriptiveness of internally (e.g., generous, polite) or externally focused traits (e.g., coffee drinker) about *themselves* or a *close other* (the participant's mother), and found no significant group differences in Self>Other activation. However, as the "other" person in this study was someone significantly close to the participant, the lack of group differences in this study may reflect a simple absence of any Self>Other effects in the control group. Research with typical adults shows that the vMPFC Self>Other response is most robust when the comparison "other" is a familiar but *non-close other* (Kelley et al., 2002). In contrast, when the other person is a *close other* (Ochsner et al.,

2005) or someone *similar to oneself* (Mitchell et al., 2006), vMPFC response to Self and Other is nearly identical. Given that the vMPFC is highly involved in tracking self-relevant information (Moran et al., 2006), the vMPFC may be picking up on self-relevant information even when one is directed to think about others.

Another reason for the lack of a vMPFC group difference in the Kennedy and Courchesne (2008a) study may be a more pronounced egocentrism in ASC (Frith & de Vignemont, 2005). Clinical accounts from the outset, by Kanner (1943) and Asperger (1944), suggested an extreme egocentrism in autism. A study by Mitchell and O'Keefe (2008) documented that typically developing children tend to attribute more privileged self-knowledge to themselves, over and above that which they think their mother knows of them. However, people with ASC perceive themselves and their mothers to know equivalent amounts of information about themselves. These observations suggest that individuals with ASC may not automatically distinguish between self and other (Lombardo & Baron-Cohen, 2010).

Testifying to this explanation, our own study (Lombardo, Chakrabarti, Bullmore, Sadek et al., 2010) compared activation when participants made mentalizing or physical judgments about themselves or a familiar but non-close other (the British Queen). While control participants showed robust effects for Self>Other judgments in vMPFC, participants with autism showed equivalent activity in vMPFC for both Self and Other judgments. Corroborating that this lack of a neural self-other distinction is associated with social deficits, we showed that the magnitude of social impairment as measured on the Autism Diagnostic Interview–Revised (ADI-R) increased as the self-other distinction in the vMPFC decreased.

Further evidence in real-time social contexts also suggests that the normative neural response for self-referential processing is atypical in ASC. Chiu and colleagues (2008) assessed agent-specific responses in the neural systems underlying decision-making in a social context (i.e., the trust game). Participants with autism showed marked reduction in an area previously shown to be sensitive specifically for self-decisions in the context of a social interaction; the middle cingulate cortex (MCC). The magnitude of MCC self-response was also strongly related to the social impairments in ASC. However, given the embedding of this task in a real-time social interaction, it is difficult to tell from this study whether the effects observed during the self-decision phase may relate to deficits in self-mentalizing, other-mentalizing, or a combination of both (Frith & Frith, 2008). Our own study (Lombardo, Chakrabarti, Bullmore, Sadek, et al., 2010) clarifies this issue, showing that participants with autism do indeed hypoactivate the MCC specifically for self-mentalizing when compared to other-mentalizing.

In sum, cognitive impairments in theory of mind are robust and consistent in ASC and occur for both self and other. False belief ability is significantly delayed by about 5 years, and even when individuals with ASC acquire such abilities, subtle deficits still exist. In this sense, theory of mind deficits could be universal to individuals on the autistic spectrum, regardless of IQ level or language level. Even in high-functioning individuals with ASC, clear signs of theory of mind deficits remain in natural, implicit mentalizing and complex emotion perception.

From our review of the neural systems involved in theory of mind in autism, the dMPFC seems a consistent, replicable locus of abnormal neural function during theory of mind tasks that are more conceptual or require linguistic processing. However, given the wide variety of findings in the neuroimaging literature, it is difficult to say whether there is a consistent picture of atypical neural function in other regions of the brain and across a myriad of mentalizing tasks. As we have highlighted, the range of paradigms extends from visual stimuli of faces, cartoons, or ambiguous geometric shapes, to linguistic scenarios, reflective judgments, and competitive games embedded in a social context. Furthermore, the social target about whom inferences are made varies across the self and real or hypothetical others. Greater clarity among this range of stimuli, tasks, and social targets can be made via quantitative meta-analysis.

Neural Systems Involved in ASC Social Impairment

To surmount the limitations of qualitative reviews of the neural systems underlying social behavior in ASC, we recently conducted a voxel-wise whole-brain quantitative meta-analysis of all neuroimaging studies in autism to date. Collapsing across all kinds of social tasks (e.g., biological motion, face perception, emotion, theory of mind, imitation, self-referential cognition), hypoactivation in ASC occurs across a whole neural circuit implicated in the typical development of social cognition; namely the vMPFC, dMPFC, FO, anterior insula (AI), amygdala (Amyg), anterior temporal lobe (ATL),

mid and posterior sections of the superior temporal sulcus (mSTS, pSTS), secondary somatosensory cortex/inferior parietal lobe (SII/IPL), and fusiform gyrus (FG). See Figure 55.2. That is, across the entire literature of "social" functional neuroimaging studies in autism, individuals with ASC consistently show reduced activation in this crucial network involved in normative social cognition.

We followed up this "social" meta-analysis by dividing studies into theory of mind studies or face-processing studies (here, face-processing included all studies using faces irrespective of the emotional context). Theory of mind studies highlighted a hypoactive neural circuit in ASC within the dMPFC, posterior cingulate/precuneus (PCC), pSTS, and ATL (see blue clusters in Figure 55.3a), while face-processing in ASC highlighted a nearly dissociable hypoactive circuit of Amyg, AI, and FO (see orange clusters in Figure 55.3a).

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We suggest that these striking dissociations, taken together, reflect neural endophenotypes that index impairment in specific social domains. Initial validity for this suggestion comes from the observation that the neural systems crucial for normative theory of mind processes such as pSTS, ATL, dMPFC, and PCC (Frith & Frith, 2003; Saxe & Powell, 2006) all are areas of consistent hypoactivation for theory of mind in ASC, but not for face processing. In contrast, the amygdala, FO, and insula tend to be involved in emotion and facial emotion processing (Lee & Siegle, 2009; Wager et al., 2008).

~~Two of the distinct face-processing regions (FO and amygdala) have already been observed as possible endophenotype candidates.~~ Our own early work demonstrated that people with ASC show reduced activity in FO during the RMET (Baron-Cohen et al., 1999). In later work we showed that parents of individuals with autism manifest a similar neural response profile (Baron-Cohen et al., 2006). Individual differences in trait empathy in the general population covary with activity in FO during facial emotion recognition and such relationships generalize regardless of the type of emotion (Chakrabarti, Bullmore, & Baron-Cohen, 2006) and across development (Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008). Furthermore, as mentioned earlier, performance on the RMET is impaired in parents and siblings of children with autism and may thus be a useful cognitive endophenotypic marker of social symptoms related to autism (Baron-Cohen & Hammer, 1997; Dorris, Espie, Knott, & Salt, 2004; Losh & Piven, 2007; Losh et al., 2009).

When participants performed the RMET in the scanner, we also found significantly reduced amygdala activity in ASC—an impetus for the amygdala theory of ASC (Baron-Cohen et al., 2000). Similarly for the amygdala, clinically unaffected siblings of children with autism exhibit intermediate activation between autistic and normal levels during face-processing (Dalton, Nacewicz, Alexander, & Davidson, 2007). The convergence of previous research with the meta-analytic result here suggests the FO and amygdala as initial endophenotypic markers of autistic deficits in face processing and emotion recognition. However, unlike the FO and amygdala, within the theory of mind system no neuroimaging studies have specifically looked for heritability or familiality of functioning. Future work should specifically address this question.

Despite this dissociation of neural systems involved in theory of mind and face-processing, we also found that the vMPFC emerged as the only *common* hypoactive region for both theory of mind and face-processing. This common area of the vMPFC may be of crucial importance in the search for neural endophenotypes of social dysfunction in autism. The vMPFC is a hub for social information processing in the typically developing brain (Amodio & Frith, 2006) and is important for self-referential processing and understanding the relationship between self and other (Mitchell et al., 2006; Ochsner et al., 2005). In a recent study we found that in autism, the vMPFC does not distinguish between self and other and this lack of distinction is related to the social impairments in autism (Lombardo, Chakrabarti, Bullmore, Sadek et al., 2010).

Aside from its role in cognition, vMPFC is also a network hub for intrinsic functional brain organization (Buckner et al., 2009) and connects much of the prefrontal cortex with subcortical limbic areas (Hagmann et al., 2008). ~~The role of the vMPFC in this normative organization and as an area with tonically increased baseline activity is perturbed in autism~~ (Kennedy & Courchesne, 2008b; Kennedy, Redcay, & Courchesne, 2006). Dopamine and serotonin binding in MPFC is also reduced in autism (Ernst, Zametkin, Matochik, Pascualvaca, & Cohen, 1997; Makkonen et al., 2008; Murphy et al., 2006), as are glucose metabolism (Hazlett et al., 2004; Haznedar et al., 2000) and regional cerebral blood flow (George et al., 1992; Zilbovicius et al., 1995). Concentrations of metabolites such as choline, which reflect cell membrane metabolism, are reduced in the area in ASC (Levitt et al., 2003).

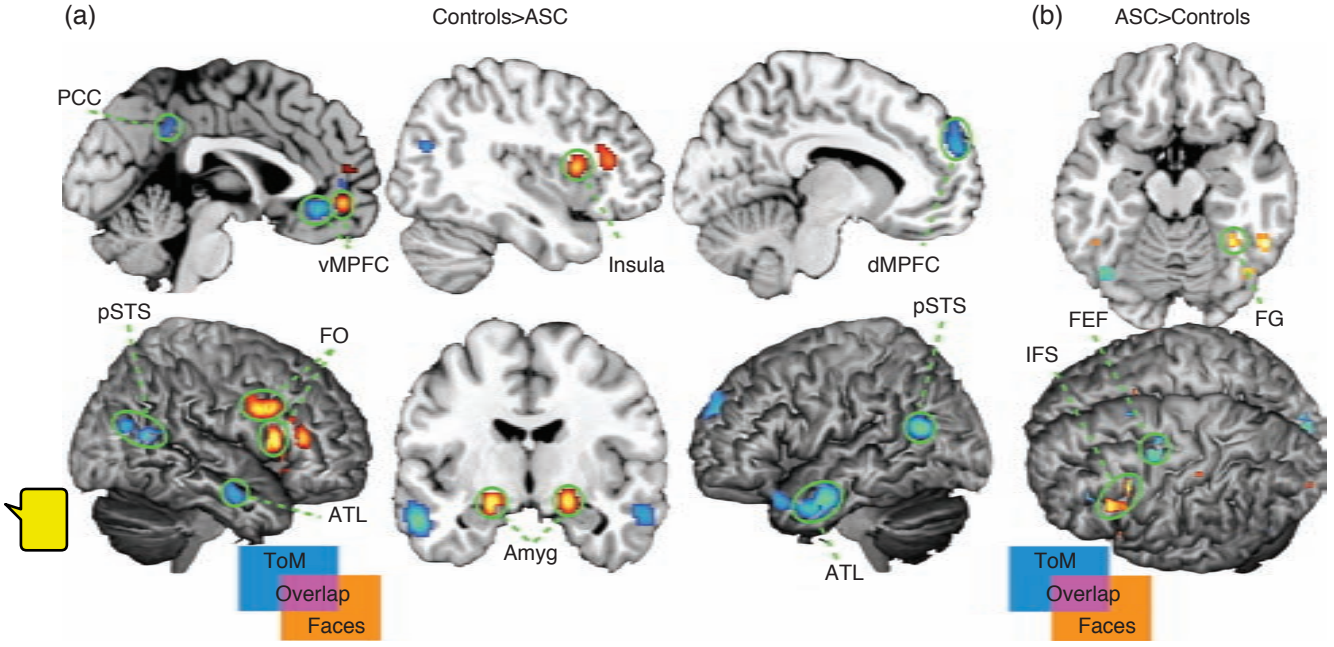

Fig. 55.2 Areas identified in the social meta-analysis. Controls>ASC (orange), ASC>Controls (blue).

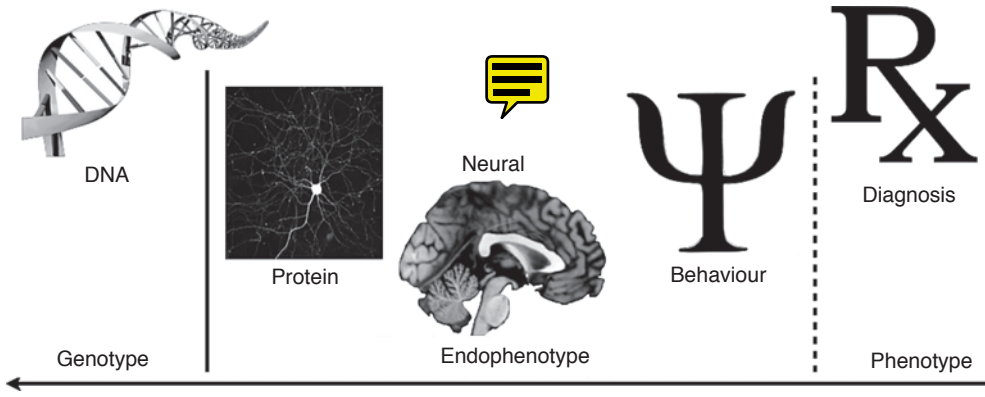

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Fig. 55.3 Areas identified in the face processing (orange) and theory of mind (blue) meta-analysis. Panel a) shows the results for Controls>ASC. Panel b) shows the results for ASC>Controls.

White matter adjacent to the vMPFC shows reduced fractional anisotropy, tract number (Barnea-Goraly et al., 2004; Cheung et al., 2009; Pardini et al., 2009, Pugliese et al., 2009), and white matter volume (Bonilha et al., 2008; McAlonan et al., 2009), while gray matter volume is increased in the vMPFC of individuals with autism (Bonilha et al., 2008; Carper & Courchesne, 2005; ~~McAlonan et al., 2005;~~ Waiter et al., 2004). The convergence of both the cognitive and biological significance of the vMPFC, both in social functioning and in general network organization suggests that the vMPFC is an important network node that future research in autism should target.

In contrast to hypoactivations, during social information processing individuals with ASC may be compensating for the lack of normative engagement of social cognitive circuits by hyperactivating other areas of the brain. Our meta-analyses found evidence of such compensatory hyperactivation in the dorsal premotor cortex near the frontal eye fields (FEF) for theory of mind and in the inferior frontal sulcus (IFS) and right FG for face processing. FEF and IFS are integral areas of a hierarchical cognitive control circuit (Badre, 2008; Corbetta, Patel, & Shulman, 2008; Derrfuss, Brass, Neumann, & von Cramon, 2005). Given that high-functioning individuals with autism have certain strengths in nonsocial cognitive processing (Baron-Cohen, Richler, Bisarya, Gurunathan, & Wheelwright, 2003; Mottron, Dawson, Soulières, Hubert, & Burack, 2006), these results suggest nonsocial cognitive strategies may be ~~being~~ co-opted to solve problems of social information processing (Belmonte et al., 2004). These meta-analytic results are consistent with other recent findings (Belmonte, Gomot, & Baron-Cohen, 2010) contradicting the idea that people with autism always have abnormally low frontal activity and abnormally greater posterior cortical activity. Rather we suggest the more general notion that people with autism deploy alternate strategies to solve cognitive problems, via routes that may be more readily available to them than those used by typical individuals.

In conclusion, autistic abnormalities in theory of mind and face processing arise in brain regions implicated in normative functioning. The decreased recruitment of these systems is nearly completely distinct between theory of mind and face processing tasks. The exception is a common region in vMPFC, consistently hypoactivated across both theory of mind and face processing. Emerging research suggests that vMPFC may be a network hub on both cognitive and biological levels. We suggest that future work examine the possibility of reduced vMPFC response as a meaningful physiological marker for general social impairment in autism (the meta-analysis maps are available upon request). In addition, the dissociable neural systems involved in theory of mind and face processing may be meaningful biomarkers or endophenotypes for specific social subdomains. Such anatomically and functionally circumscribed endophenotypes may greatly aid genetic association studies in humans, ~~to~~ parallel ~~the~~ basic research on animal models of social behavior. ~~In final section,~~ we provide a brief overview of genetic underpinnings of social behavior, and suggest the utility of such endophenotypes for future genetic research.

The Genetics of Social Behavior: Implications for a Neural Endophenotype for Autism

Confirming the known familiality of social behavior in ASC (Adolphs, Spezio, Parlier, & Piven, 2008; Baron-Cohen & Hammer, 1997; Baron-Cohen et al., 2006; Dorris, Espie, Knott, & Salt, 2004; Losh & Piven, 2007; Losh et al., 2009), recent research has begun to pinpoint its genetic underpinnings. Animal research suggests that basic forms of social behavior such as maternal and pair-bonding behavior have a long evolutionary history across many species. Some of these genetic mechanisms are common across species, and hence relevant to understanding social behavior in humans. The combination of knowledge of human genetic variability and techniques such as fMRI to study whole-brain activity in living humans are poised to enable a parsing of the genetic factors giving rise to complex social behaviors. To do this, it is crucial to have well-defined phenotypic measures. ~~Given that neural measures are often more sensitive than behavioral ones~~, well-defined "neural" phenotypes, as described in the previous section, represent a concrete step towards such future research (Landis & Insel, 2008).

Several studies have explicitly investigated the genetic basis of human social behavior in the general population. A standard approach so far has been to test for heritability (see Box 55.3) of trait empathy or other measures of social behavior by comparing monozygotic (MZ) and dizygotic (DZ) twins. Nearly all of these studies have shown a greater correlation of empathy measures in MZ compared to DZ twins, suggesting a genetic basis for trait empathy (Davis, Luce, & Kraus, 1994; Loehlin & Nichols, 1976; Matthews, Batson, Horn, & Rosenman, 1981) as measured indirectly using the Questionnaire Measure of Emotional Empathy (QMEE) (Mehrabian & Epstein, 1972). Rushton et al. (1986), in a large-scale twin study in humans, suggested a heritability estimate of 68% for emotional empathy. Other twin studies, particularly in children, have used behavioral observation paradigms of empathy in a laboratory situation. These involve simulating scripted situations (e.g., the experimenter tripping on a chair, or the mother of the child getting her finger caught while closing a suitcase), while video-recording the child's reactions. A study of 14- and 20-month-old twins using this paradigm confirmed a genetic contribution to empathic concern (Zahn-Waxler, Radke-Yarrow, Wagner, & Chapman, 1992).

A recent twin study on 409 twin pairs by the same group showed that genetic effects on empathy and prosociality (measured using video-recorded behavior in a laboratory setting) increase with age and shared environmental effects decrease with age (Knafo, Zahn-Waxler, Van Hulle, Robinson, & Rhee, 2008). In the domain of autistic traits, very few behavioral phenotypes have been tested for genetic effects. A notable exception is performance on the RMET, which shows a strong degree of familiality (Baron-Cohen & Hammer, 1997; Losh & Piven, 2007). Recent questionnaire measures of social (Social Responsiveness Scale (SRS); Constantino & Todd, 2000, 2005) and emotion understanding (alexithymia; Szatmari et al., 2008), and autistic traits (Autism Spectrum Quotient (AQ); Baron-Cohen et al., 2001b) reveal strong familiality (Bishop et al., 2004) as well as heritability in twin studies (Hoekstra et al., 2007). These studies corroborate findings from the early twin studies in suggesting a genetic underpinning for social behavior relevant to ASC.

In comparison, the animal phenotypes for social behavior have primarily included indices of maternal care (e.g., licking-grooming/arched-back nursing), pair bonding behavior (e.g., mate loyalty), and social recognition. These have established a role for a set of genes involved in endogenous opioid systems (Panksepp, 1998; Panksepp, Nelson, & Bekkedal, 1997), neuroendocrine factors such as oxytocin and vasopressin (Donaldson & Young, 2008; Winslow & Insel, 2004), and sex hormones such as estrogen (Choleris, Clipperton, Phan, & Kavaliers, 2008), among others. A recent study reported testing for "empathy" in rats by measuring autonomic changes in rats who observed other rats receiving electric shocks (Chen, Panksepp, & Lahvis, 2009). This study showed that such an autonomic index of "empathy" was a function of the genetic background. Developing effective assays for social behavior and empathy in rodents continues to be an

Box 55.3. Heritability

Heritability refers to the proportion of the variance in a particular phenotype that is explained by purely genetic effects. Experiments with monozygotic (MZ) and dizygotic (DZ) twin pairs are used to estimate the heritability of particular traits. In these experiments, heritability is estimated after accounting for phenotypic variance due to shared and nonshared environments.

active area of research (Arakawa et al., 2008; Crawley, 2007). However, there is considerable variation in the degree to which gene function is preserved across species. A common example is vasopressin, which in monogamous species of voles is involved in pair-bonding behavior such as mate-guarding and paternal care, but has no such effect in non-monogamous species of voles. Hence, whilst animal research can point toward suggestive candidate genes for social behavior, it is essential to test for genetic association with relevant human social behavioral endophenotypes.

Processing facial expressions of emotion is one of the key paradigms used to test social behavior in an experimental setting (See Table 55.1 for examples of such studies). Initial studies associating candidate gene polymorphisms with neuroimaging paradigms of facial expression processing have shown considerable promise. Hariri and colleagues (2005; 2002) showed that variability in serotonin transporter (*SLC6A4*) genotype modulates amygdala response to fear faces. Using the same paradigm, Meyer-Lindenberg and colleagues (Meyer-Lindenberg et al., 2009) showed that polymorphisms in the arginine vasopressin receptor 1A (*AVPR1A)* gene (previously linked to autism) are related to the amygdala response to faces displaying fear or anger. Work from our and other groups has shown that variations in the cannabinoid receptor (*CNR1*) gene modulate striatal response to happy faces (Chakrabarti, Kent, Suckling, Bullmore, & Baron-Cohen, 2006; Domschke et al., 2008). Future research will target such discrete "neural phenotypes" in ASC in combination with ideal candidate genes. Specifically, response from the regions identified in the meta-analysis should be analyzed for association with polymorphisms in these genes and others that have been linked to ~~autism spectrum conditions~~ (for a review, see Abrahams & Geschwind, 2008).

In one of the first genetic association studies of empathy (measured using EQ) and autistic traits (measured using AQ) in the general population and Asperger syndrome, we found nominally significant associations for 27 genes (Chakrabarti et al., 2009). These genes belong to three broad functional categories: a) social emotional responsivity; b) neural growth and connectivity; and c) sex steroid synthesis, transport, and metabolism. Genes involved in social/emotional responsivity included genes coding for oxytocin and its receptor (*OXT*, *OXTR*), confirming their previously reported role in ASC (Wu et al., 2005) as well as animal models of social behavior (Insel, Brien, & Leckman, 1999). Genes in the group b included those coding for neuroligin receptors (particularly, *NLGN4X*), as well as neurotrophic receptor kinases (*NTRK1*), which play a central role in neuronal survival, development, and synapse stabilization. The estrogen receptor gene (*ESR2*) as well as genes involved in the functioning of sex steroids such as *CYP11B1*, and *CYP17A1* were among the significantly associated genes in group c. These genes are among the many possible candidates to explore in relation to neuroimaging endophenotypes of social behavior as discussed in the previous section.

Conclusion

In summary, we have reviewed evidence demonstrating that people with ASC have significant social deficits across development. Underlying these deficits are abnormalities across neural circuits crucial for normative social behavior. We have also reviewed evidence suggesting that social behavior has a strong genetic component. What is needed next, both in the context of normative development and in the context of the autism spectrum and other developmental conditions, is an exploration of the processes and interactions that mediate the effects of such genetic and molecular factors on social behavior. The intervening level between genetic influences and behavioral outcomes is the neural abnormalities consistently associated with social behavior in autism. In this chapter we have identified circumscribed neural systems whose atypical response in social behavioral paradigms can function as putative neural endophenotypes. These data pave the way for future genetic association studies, both for ASC as well as in the general population. Such inquiries will strengthen our understanding of neural processes underlying social cognition in autism, and provide fundamental insights into how variation within the general population can lead to extremes such as autism.

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Note

1 The term "mentalizing" is used synonymously with the term "theory of mind."

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