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Defining the broader phenotype of autism: Genetic, brain, and behavioral perspectives

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Abstract
Achieving progress in understanding the cause, nature, and treatment of autism requires an integration of concepts, approaches, and empirical findings from genetic, cognitive neuroscience, animal, and clinical studies. The need for such integration has been a fundamental tenet of the discipline of developmental psychopathology from its inception. It is likely that the discovery of autism susceptibility genes will depend on the development of dimensional measures of broader phenotype autism traits. It is argued that knowledge of the cognitive neuroscience of social and language behavior will provide a useful framework for defining such measures. In this article, the current state of knowledge of the cognitive neuroscience of social and language impairments in autism is reviewed. Following from this, six candidate broader phenotype autism traits are proposed: (a) face processing, including structural encoding of facial features and face movements, such as eye gaze; (b) social affiliation or sensitivity to social reward, pertaining to the social motivational impairments found in autism; (c) motor imitation ability, particularly imitation of body actions; (d) memory, specifically those aspects of memory mediated by the medial temporal lobe–prefrontal circuits; (e) executive function, especially planning and flexibility; and (f) Language ability, particularly those aspects of language that overlap with specific language impairment, namely, phonological processing.

The need for integrating information across multiple levels of analysis is well illustrated by the study of autism. Current efforts toward understanding the nature, etiology, and treatment of autism involve collaboration among many scientists from multiple disciplines, each with its own perspective, method of inquiry, and scientific methods. This article, which was written collaboratively by scientists trained in developmental psychology and neuropsychology, psychiatry, bioengineering, radiology, biochemistry, and genetics, demonstrates both the challenges and benefits of such an undertaking. Autism is a severe, chronic developmental disorder which is characterized by impairments in social and communicative behavior and a restricted range of activities and interests. This puzzling and complex disorder poses basic questions about the biological bases of social behavior and relationships. How is it possible that a child can come into the world lacking the ability to engage in the most fundamental aspects of social behavior, such as making eye contact, responding to another's emotional cues, and having an understanding of what other people think and feel? To understand autism, we must comprehend how we have come to be social beings and, further, how differences in our biological makeup translate into variations in our social behavior. This is a daunting task. Over the past six decades since

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Kanner (1943) first defined autism, we have made some progress. We have learned that autism is not caused by faulty parenting, as was theorized in the 1960s (Bettelheim, 1967). We now know that autism is the manifestation of abnormal brain development and have discovered important clues regarding several brain regions that may be affected (Bailey, Luther, Dean, Harding, Janota, Montgomery, Rutter, & Lantos, 1998; Bauman & Kemper, 1994). We also have evidence that that this abnormal brain development is a consequence of both genetic and environmental factors (Bailey, Phillips, & Rutter, 1996).

We must understand not only how this syndrome could come about, but also how we can treat it effectively. Here, too, we have made some progress. Whereas previously we believed that the long-term prognosis for individuals with autism was extremely poor, we now know that early intensive behavioral interventions designed to stimulate and perhaps even restructure brain development can have a positive impact on many children with autism (Dawson & Osterling, 1997; Rogers, 1998). Many children who receive such early interventions go on to lead productive, fulfilled lives and develop meaningful relationships with others. Individuals such as Temple Grandin (Grandin, 1986), a highly successful adult with autism, have taught us much about the resilience of some individuals with autism. At the same time, other children with autism who receive intensive early intervention fail to have a dramatic response; indeed, 25% of individuals with autism remain mute for their entire lives (Lord & Paul, 1997). We have yet to explain this tremendous variation in outcome in autism. Answers to this question will shed light on the nature of brain plasticity in early development, especially those factors that promote versus constrain plasticity.

Once believed to be a rare disorder, it is now recognized that the prevalence rates for autism may be as high as 1/1000 (Bryson, Clark, & Smith, 1988; Fombonne, 1999; Gillberg & Wing, 1999) or even higher (Arvidsson, Danielsson, Forsberg, Gillberg, & Johansson, 1997; Bryson, 1996; Kadesjo, Gillberg, Hagberg, 1999; Rapin, 1997). Recent advances in developmental psychology, child psychopathology, neuropsychology, biological psychiatry, neurobiology, and genetics hold promise for shedding light on the nature and etiology of autism. A deep understanding of complex mental disorders, such as autism, requires integration of information across many scientific fields, if we are to avoid the plight of the proverbial blind men and the elephant. Each field provides a unique and important perspective, as well as specialized scientific techniques, all of which must be integrated to form a coherent whole. Communication across scientific domains and the integration of different types of information at multiple levels of analysis pose new and difficult conceptual and methodological challenges. In this paper, we examine autism at several levels of analysis, from genetics to brain to behavior, and apply this knowledge to address the question of how to define the broader autism phenotype. We hope to show that it is critical that all these levels of analysis be considered together to yield a fuller understanding of the cause, nature, and treatment of autism. What we learn about genes and the brain informs and constrains our theories about behavior and vice versa.

We begin with a brief overview of what is known about the role of genetics of autism. Following this, we make the argument that progress in the genetics of autism will benefit from the development of dimensional measures of autism traits, which will depend on a refined cognitive neuroscience of autism and social behavior. We then review some of what we know about the cognitive neuroscience of social and language impairment in autism. Finally, we propose candidate core measures of the autism behavioral phenotype, specifically in the domains of social and language impairment, that might be useful in discovering the genes involved in autism.

Genetics of Autism

Beginning with Folstein and Rutter's classic work, several twin studies provide strong support for genetic factors in autism (Folstein &

Rutter, 1977; Ritvo, Jorde, Mason–Brothers, Freeman, Pingree, Jones, McMahon, Jensen, & Mo, 1989). Folstein and Rutter found that 4 of 11 monozygotic (MZ) twins were concordant for autism whereas none of the dizygotic (DZ) twin pairs ($n = 10$) was concordant. In addition, the nonautistic MZ twins exhibited milder forms of cognitive impairment. When the presence of severe language delay, marked reading disability, persistent articulation disorder, and/or mental handicap was considered, concordance rates were 82% in the MZ twins and 10% in the DZ twins. In a later study that used a larger sample, Bailey, Le Couteur, Gottesman, Bolton, Simonoff, Yuzda, and Rutter (1995) found that the concordance rate was 69% for MZ twins and 0% for DZ twins. Other studies have shown similar discrepancies between MZ and DZ concordance rates (Ritvo et al., 1989; Steffenburg, Gillberg, Hellgren, Andersson, Gillberg, Jakobsson, & Bohman, 1989). The existence of discordant MZ twins indicates that environmental factors (infectious agents, toxins, trauma, pre-, peri-, and postnatal factors) also play a role in the etiology of autism.

The reported sibling risk rates range from 2.8 to 7.0% (see Smalley, Asarnow, & Spence, 1988, for a review). In the largest family history study, comprising 580 siblings, 4.5% were affected (7 and 14.5% for males and females, respectively), a much larger percentage than expected for the general population. The rate of autism found in relatives more distant than siblings is extremely low (Delong & Dwyer, 1988; Jorde, Mason–Brothers, Waldmann, & Ritvo, 1990; Jorde, Hasstedt, Ritvo, Mason–Brothers, Freeman, Pingree, McMahon, Peterson, Jenson, & Mo, 1991). The rapid decrease in risk rates from identical twins to siblings to more distant relatives suggests that there is a high likelihood of epistatic effects involving interactions among several genes (estimated to be between 5 and 10 or more) (Pickles, Bolton, Macdonald, Bailey, Le Couteur, Sim & Rutter, 1995; Risch, Spiker, Lotspeich, Nouri, Hinds, Hallmayer, Kaladjieva, McCague, Dimiceli, Pitts, Nguyen, Yang, Harper, Thorpe, Vermeer, Young, Hebert, Lin, Ferguson, Chiotti, Wieseslater, Rogers, Salmon, Nicholas, Petersen, Pingree, McMahon, Wong, Cavallisforza, Kraemer, & Myers, 1999).

Siblings who do not meet criteria for autism have elevated rates of a variety of autism-related symptoms. Bolton, MacDonald, Pickles, and Rios (1994) found that approximately 10–20% of siblings exhibit the broader autism phenotype, which includes language, learning, communication, and social impairments. Piven and colleagues (Piven, Palmer, Jacobi, Childress, & Arndt, 1997; Piven, Palmer, Landa, Santangelo, Jacobi, & Childress, 1997) used a family history method to examine rates of social and communication deficits and stereotyped behaviors in relatives ascertained through two autistic siblings, in comparison with rates in relatives of Down syndrome probands. Higher rates of social and communication deficits and stereotyped behavior were found in the relatives in the families with multiple-incidence autism. Recently, Piven (2001) reported that parents from multiple-incidence autism families tend to have (a) elevated rates of particular personality traits (e.g., aloof, rigid, anxious); (b) fewer close friendships than typical adults; (c) communication deficits, especially a history of language delay and pragmatic language deficits; and (d) cognitive deficits in performance IQ and executive function. Another recent study by Murphy, Bolton, Pickles, Fombonne, Piven, and Rutter (2000) reported data on personality traits of adult relatives of 99 autistic and 36 Down syndrome probands, using the Modified Personality Schedule. Factor analysis revealed three broad groups of traits, two of which ("withdrawn" and "difficult") appeared to reflect impairments in social functioning. A third group of anxiety-related traits ("tense") may be related to the burden associated with raising a child with autism, whereas the withdrawn factor appears to be a manifestation of the liability to autism. Other studies identified elevated rates of specific language and social impairments in family members, including impairments on tests of executive function, especially set shifting and planning (Hughes, Plumet, & Leboyer, 1999), reading ability, including passage comprehension and

rapid automotized naming (Piven & Palmer, 1997); and pragmatic language (Landa, Piven, Wzorek, Gayle, Chase, & Folstein, 1992). These data suggest that studies that incorporate quantitative measures of autistic traits that may be expressed in milder forms in relatives might be useful in studying the genetic basis of autism.

Several linkage studies have now been conducted (Alarcon, Cantor, Liu, Gilliam, & Geschwind, 2002; Ashley–Koch, Wolpert, Menold, Zaeem, Basu, Donnelly, Ravan, Powell, Qumsiyeh, Aylsworth, Vance, Gilbert, Wright, Abramson, Delong, Cuccaro, & Pericak–Vance, 1999; Bailey, 1998; Barrett, Beck, Bernier, Bisson, Braun, Casavant, Childress, Folstein, Garcia, Gardiner, Gilman, Haines, Hopkins, Landa, Meyer, Mullane, Nishimura, Palmer, Piven, Purdy, Santangelo, Searby, Sheffield, Singleton, Slager, Struchen, Svenson, Vieland, Wang, Winklosky, 1999; Bradford, Haines, Hutcheson, Gardiner, Braun, Sheffield, Cassavant, Huang, Wang, Vieland, Folstein, Santangelo, & Piven, 2001; Buxbaum, Silverman, Smith, Kilifarski, Reichert, Hollander, Lawlor, Fitzgerald, Greenberg, & Davis, 2001; International Molecular Genetic Study of Autism Consortium, 2001; Liu et al., 2001; Philippe, Martinez, Guilloudbataille, Gillberg, Rastam, Sponheim, Coleman, Zappella, Aschauer, Vanmalldergerme, Penet, Feingold, Brice, & Leboyer, 1999; Risch et al., 1999). Candidate autism susceptibility regions include chromosomes 1p, 2q, 7q, 13q, 16p, and 19q. However, the linkage signals have generally been small, and findings have not been consistently replicated across studies. Chromosome 7 may be the exception, with three different groups reporting positive results (Ashley–Koch et al., 1999; Barrett et al., 1999; International Molecular Genetic Study of Autism Consortium, 2001). In a study of multiplex autism families, Bradford et al. (2001) incorporated information about proband and parent language phenotypes into linkage analyses in the two regions for which they had found highest signals in their first sibling pair genome screen, namely, chromosomes 13q and 7q, and found that the signals obtained on chromosome 7q, as well as at least one signal on chromosome 13q, were mainly attributable to the subgroup of families in which both probands had language delay. Using the same line of reasoning, Alarcon and colleagues (2002) performed a nonparametric multipoint linkage analysis with 152 families from the Autism Genetic Resource Exchange, focusing on three potential quantitative trait loci (QTLs) derived from the Autism Diagnostic Interview: "age at first word," "age at first phrase," and a composite measure of "repetitive and stereotyped behavior." They found strongest QTL evidence for age at first word on chromosome 7q.

In summary, it appears that there is not a single gene that can account for the autism syndrome. Rather, there appear to be multiple genes, each one a risk factor for a component of this complex syndrome, which, together with other genes, account for the extent of syndrome expression. These genes act as nondeterministic risk factors for the autism syndrome, with increasing risk being conferred by a greater number of genes. Moreover, it appears that susceptibility genes may have effects on a continually distributed phenotype. If this is the case, then gene discovery might be helped by the development of quantitative (i.e., dimensional) measures of components of the autism syndrome. Most linkage studies conducted to date have used the clinical diagnosis of autism to categorize individuals as affected or nonaffected. However, the use of quantitative traits representing components of the syndrome might provide more sensitivity in distinguishing which individuals are truly affected. The QTL analysis is most powerful when such phenotypic measures can identify not only those who are impaired but also those who are above average in a specific domain (i.e., extreme scores on both ends of the continuum). Phenotypic measures can be behavioral or biological (e.g., brain size, serotonin). This paper addresses the question of what might be useful quantitative behavior and/or neurocognitive measures of the autism phenotype. We focus specifically on the domains of social and language impairment (see Bolton, Pickles, Murphy, & Rutter, 1998, for a discussion of genetic factors related to repetitive behaviors in autism). We first briefly examine another complex mental disorder for which such quantitative genetic traits have

been discovered, namely, reading disability, as this example might offer a heuristic model.

Clues From the First QTL Found for a Human Behavioral Disorder

Family studies have demonstrated that reading disability runs in families (e.g., DeFries, Vogler, & LaBuda, 1986). Siblings and parents of children with reading disability perform significantly worse on reading tests than siblings and parents of children without reading disability. In a large twin study (DeFries, Fulker, & LaBuda, 1987), it was shown that 66% of MZ twins were concordant for reading disability, compared to 43% of DZ twins. Like most complex disorders, including autism, it is believed that multiple genes combined with multiple environmental factors contribute to this disability.

The first QTL for a human behavioral disorder was found for reading disability (Cardon, Smith, Fulker, Kimberling, Pennington, & DeFries, 1994). Like social and language ability, reading is a complex skill requiring many component subskills. Deficiencies in any one subdomain would be expected to impact reading ability as a whole, with greater number of deficiencies being associated with a greater likelihood of reading disability and/or more severe reading impairment. When reading is considered in terms of different component processes, distinct subdomains have been linked to different chromosomal regions. Specifically, Grigorenko, Wood, Meyer, Hart, Speed, Shuster, and Pauls (1997) found that, whereas phonological awareness was linked to chromosome 6, single-word naming was linked to chromosome 15. These authors concluded that each of these components of reading ability reflected a distinct phenotype, representing different levels in the hierarchy of reading-related skills, each of which is linked to a different chromosomal region.

If the same approach were adopted for autism, it would be necessary to identify components of social and language behavior that we believe to be affected in autism. General measures of social and language ability, such as the social subdomain score from the Vineland Adaptive Behavior Scale or verbal IQ, might be too global. The question, then, is what might be useful quantitative autism behavioral traits? We argue that an answer to this question will depend on a sophisticated understanding of the cognitive neuroscience of autism. Thus, we next consider some of what is known about the brain bases of social and language impairment in autism, and then return to the question of possible quantitative measures of autism traits.

Cognitive Neuroscience of Social and Language Impairment in Autism

Advances in neurobiology, brain imaging, and neuropsychology have yielded new insights into the possible brain basis of autism (Akshoomoff, Pierce, & Courchesne, 2002; Bailey et al., 1996; Rodier, 2002). Individuals with autism have specific impairments in processing social and emotional information (Baron–Cohen, Tager–Flusberg & Cohen, 1993; Davies, Bishop, Manstead & Tantam, 1994; Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Hobson, Ouston, & Lee, 1988a, 1988b; Klin, Sparrow, de Bildt, Cichetti, Cohen, & Volkmar, 1999; Mundy, Sigman, Ungerer, & Sherman, 1986; Smith & Bryson, 1994; Teunisse & DeGelder, 1994). Core early appearing domains of social impairments in autism include social orienting (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Dawson, Toth, Abbott, Osterling, Munson, & Estes, 2002), joint attention (Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Mundy et al., 1986), responses to the emotional displays of others (Sigman, Kasari, Kwon, & Yirmiya, 1992), and face recognition (Dawson, Carver, Meltzoff, Panagiotides, McPartland, & Webb, 2002; Klin et al., 1999). These social impairments, many of which are apparent by 1 year of age (Osterling & Dawson, 1994; Osterling, Dawson, & Munson, 2002), suggest that autism is related to dysfunction of early developing brain systems involved in social cognition (Baron–Cohen, Ring, Bullmore, Wheelwright, Ashwin, & Williams, 2000; Baron–Cohen, Wheelwright, Bullmore, Brammer, Simmons, & Williams, 1999; Dawson, 1996).

Animal, human lesion, and neuroimaging

studies have identified several brain regions that are important for social cognition, including temporal lobe areas (e.g., fusiform gyrus, superior temporal sulcus or STS, and entorhinal cortex) and associated nuclei (amygdalae and hippocampi), prefrontal cortex (PF, especially the ventromedial PF cortex and Broca's area), and inferior parietal cortex (Bachevelier, 1994; Barbas, 1995; Brothers, Ring, & Kling, 1990; Chaminade, Meltzoff, & Decety, 2002; Damasio, 1994; Decety, Chaminade, Grezes, & Meltzoff, 2002; LeDoux, 1994; Rolls, 1990; Williams, Whiten, Suddendorf, & Perrett, 2001).

Several neuropathological and neuroanatomical studies have identified abnormalities in the medial temporal lobe (MTL) region and cerebellum within autistic samples, although these findings have not been replicated in all studies. Neuropathological studies have variably shown increased cell densities and reduced cell size in the MTL and other structures, as well as reduced numbers of Purkinje cells in the cerebellum (Bailey et al., 1998, Bauman & Kemper, 1994; Raymond, Bauman, & Kemper, 1996). One of the more consistent neuroanatomic findings associated with autism has been evidence of increased cerebral volume or brain weight (Bauman & Kemper, 1985, 1994; Bailey et al., 1998; Hardan, Minshew, Mallikarjuhn, & Keshavan, 2001; Piven, Arndt, Bailey, & Andreasen, 1996; Piven, Arndt, Bailey, Havercamp, Andreasen, & Palmer, 1995; Sparks, Friedman, Shaw, Aylward, Echelard, Artu, Maravilla, Giedd, Munson, Dawson, & Dager, in press). Evidence of differential brain enlargement found in young, but not older, children or adults with autism suggests that increased brain volume may be age related and reflect accelerated developmental processes early in the clinical course of autism (Akshoomoff et al., 2002; Courchesne, Karns, Davis, Ziccardi, Carper, Tigue, Chisum, Moses, Pierce, Lord, Lincoln, Pizzo, Schreibman, Haas, Akshoomoff, & Courchesne, 2001). However, postmortem and imaging findings of brain enlargement have also been observed in older individuals with autism, suggesting that the developmental course within individuals may be quite variable (Bailey et al., 1998; Bauman & Kemper, 1985; Courchesne, Muller, & Saitoh, 1999; Lainhart, Piven, Wzorek, Landa, Santangelo, Coon, & Folstein, 1997; Piven et al., 1995, 1996).

Sparks et al. (in press) examined volumes of the cerebrum, cerebellum, amygdala, and hippocampus in 3- to 4-year-old children with autism spectrum disorder (ASD), compared to age-matched control groups of typically developing (TD) children and developmentally delayed (DD) children. Children with ASD were found to have significantly increased cerebral volumes, compared to TD and DD children. Cerebellar and MTL (amygdalae and hippocampi) volumes for the ASD group were increased compared to the TD group, but they were proportional to the overall increases in cerebral volume. In the subgroup of ASD children with strictly defined autism, enlargement of the amygdala was found to be in excess of increased cerebral volume. Preliminary analyses of neuropsychological correlates suggest that increased amygdala size is associated with greater impairment of joint attention, a core autistic symptom. Howard and coworkers (Howard, Cowell, Boucher, Broks, Mayes, Farrant, & Roberts, 2000) also found that impaired recognition of facial expressions was correlated with enlarged amygdala volume. Thus, increased amygdala volume may be a marker of severity of autism impairment.

Evidence for the involvement of the ventromedial PF cortex in autism is less direct. It is primarily based on findings of deficiencies in social cognition and theory of mind in patients with ventromedial PF damage (Cicerone & Tanenbaum, 1997; Damasio, Tranel, & Damasio, 1990; Stone, Baron–Cohen, & Knight, 1998) and functional magnetic resonance imaging (fMRI) studies showing activation of the ventromedial PF region during theory of mind and social attribution tasks (Fletcher, Happe, Frith, Baker, Dolan, Frackowiak, & Frith, 1995; Happe, Ehlers, Fletcher, Frith, Johansson, Gillberg, Dolan, Frackowiak, & Frith, 1996; Schultz, Romanski, & Tsatsanis, 2000). Medial PF dopaminergic activity, measured during positron emission tomography (PET) studies, has been found to

be reduced in autism (Ernst, Zametkin, Matochik, Pascualvaca, & Cohen, 1997).

Studies of MTL and PF function in young children with autism

Dawson and colleagues investigated early MTL function in autism by administering neuropsychological tasks (adapted from tasks given to nonhuman primates) to school-aged children with autism and examining their performance in relation to the severity of their autism symptoms (Dawson , Meltzoff, Osterling, Rinaldi, & Brown, 1998). Compared to developmentally matched children with Down syndrome and children with typical development, children with autism were impaired on the delayed nonmatching to sample task (DNMS). In nonhuman primates and human adults, lesions of the MTL and the ventromedial PF cortex (specifically, the orbital PF region) impair performance on the DNMS but not on spatial working memory tasks, such as the delayed response task (Bachevalier & Mishkin, 1986; Diamond & Goldman–Rakic, 1989; Kowalska, Bachevalier, & Mishkin, 1991; Meunier, Bachevalier, & Mishkin, 1997; Zola–Morgan & Squire, 1993; Zola–Morgan, Squire, & Amaral, 1989). However, children with autism also were impaired on the delayed response task. In nonhuman primates, lesions to the dorsolateral PF cortex impair performance on the delayed response task but MTL lesions do not (Diamond & Goldman–Rakic, 1986, 1989; Goldman, Rosvold, & Mishkin, 1970). The severity of autism symptoms correlated strongly with performance on the DNMS task, but not with performance on the dorsolateral PF task. Thus, although children with autism were impaired on both the MTL and PF tasks, only performance on the MTL task correlated with symptom severity.

Dawson and coworkers (Dawson, Munson, Estes, Osterling, McPartland, Toth, Carver, & Abbott, 2002) recently extended these studies to a larger and younger sample of children with ASD and administered a more comprehensive neuropsychological battery. Data were collected from 72, 3- to 4-year-old children with ASD (49 children with Autistic disorder and 23 children with Pervasive Developmental disorder, Not Otherwise Specified), 34 mental age–matched children with DD, and 39 mental age–matched TD children. It was predicted that joint attention ability, a core autism symptom, would be more closely correlated with performance on tasks tapping the MTL–ventromedial PF circuit, than with performance on tasks tapping the dorsolateral PF cortex. Three tasks assessing dorsolateral PF function (A not B, A not B with invisible displacement, and spatial reversal), three tasks assessing MTL and/or MTL–ventromedial PF function (two versions of DNMS with brief delay, and object discrimination reversal), and three tasks assessing joint attention ability were administered. The A not B task requires both working memory and response inhibition. It has been linked to the dorsolateral PF cortex, based on both human infant studies and animal lesion studies (Diamond & Goldman–Rakic, 1986, 1989; Goldman et al., 1970). Lesions to the MTL and parietal cortex in the adult animal do not disrupt performance (Diamond & Goldman–Rakic, 1989; Diamond, Zola–Morgan, & Squire, 1989). The spatial reversal task also requires both working memory (it involves maintaining the response set during a delay) and problem solving or concept formation (the child must generalize a rule in order to respond correctly) (Espy, Kaufmann, McDiarmid, & Glisky, 1999). The DNMS assesses rule-learning ability (specifically, the ability to abstract "novelty" and associate it with reward) and visual recognition memory (Diamond, Churchland, Cruess, & Kirkham, 1999). It is strongly linked to the amygdala and hippocampus in lesion studies with monkeys (Bachevalier & Mishkin, 1986; Kowalska et al., 1991; Meunier et al., 1997; Zola–Morgan & Squire, 1993; Zola–Morgan et al., 1989) and in human amnesic patients (Squire, Zola–Morgan, & Chen, 1988). The object discrimination reversal task (ODR) assesses the child's ability to modify his or her behavioral response when a particular response is no longer rewarded. Performance on ODR is severely impaired by early and late lesions to the ventromedial PF cortex, specifically the orbitofrontal region, in monkeys (Butter, 1969;

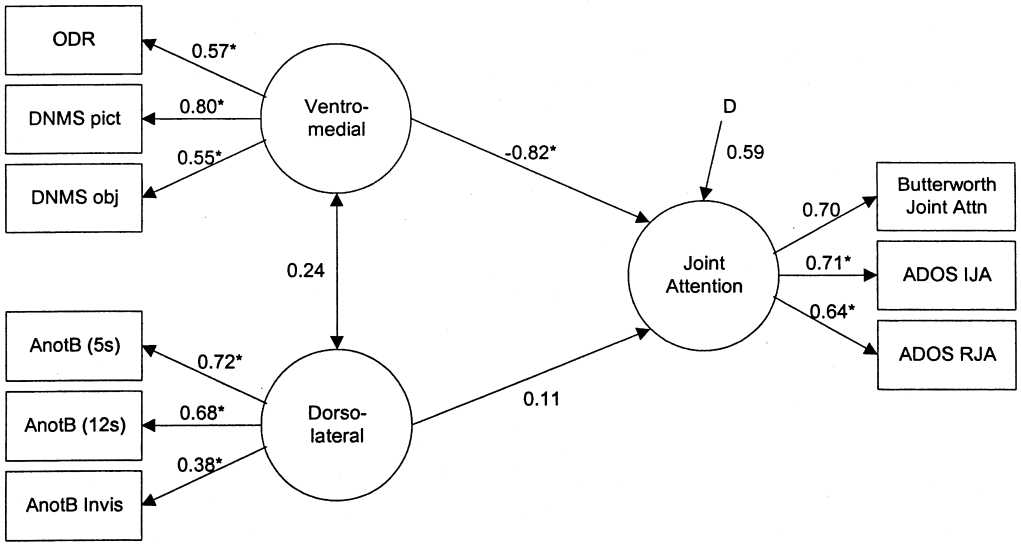

Figure 1. Structural model of the relations between joint attention and neurocognitive abilities. Medial temporal lobe and ventromedial prefrontal tasks: object discrimination reversal (ODR), delayed nonmatching to sample (DNMS) with pictures and objects. Dorsolateral prefrontal tasks: A not B with 5- and 12-s delays and A not B with invisible displacement. Joint attention tasks: experimental paradigm developed by Butterworth and Jarrett (1991), responds to joint attention from the Autism Diagnostic Observation Schedule—Generic (ADOS), initiates joint attention from the ADOS—Generic. From "Neurocognitive function and joint attention ability in young children with autism spectrum disorder," by G. Dawson, J. Munson, A. Estes, J. Osterling, J. McPartland, K. Toth, L. Carver, and R. Abbott, 2002, *Child Development, 73,* pp. 345–358. Copyright 2002 by University of Chicago Press. Reprinted with permission.

Butters, Butter, Rosen, & Stein, 1973; Goldman–Rakic, Isseroff, Schwartz, & Bugbee, 1983; Jones & Mishkin, 1972) and by lesions of the ventromedial PF region in human adults (Damasio, 1994; Damasio et al., 1990; Rolls, 1990; Rolls, Hornak, Wade, & McGrath, 1994). Dias, Robbins, and Roberts (1996) showed that in monkeys, ODR could clearly dissociate dysfunction of the ventromedial PF cortex from dysfunction of the dorsolateral PF cortex.

As expected, children with autism were severely impaired on joint attention, compared to mental age–matched children with DD and typical development. Structural equation modeling confirmed the hypothesis that, in young children with autism, performance on the MTL/ventromedial PF tasks is more strongly associated with joint attention abilities than is performance on the dorsolateral PF tasks (see Figure 1). These findings suggest that core autism symptoms may be more specifically related to dysfunction of the MTL and closely related brain regions.

MTL dysfunction: Relation to heterogeneity and downstream consequences for PF (executive) dysfunction. It has been proposed that the variability in functioning found in autism may be accounted for by differences in the extent of MTL dysfunction (Bachevalier, 1994; Barth, Fein, & Waterhouse, 1995; Dawson, 1996; Waterhouse, Fein, & Modahl, 1996). Bachevalier (1994) found that monkeys with lesions involving both the hippocampus and amygdala showed more severe memory and social impairments than those with lesions to the amygdala alone (these monkeys showed primarily social impairments). Prather and colleagues (Prather, Lavenex, Mauldin–Jourdain, Mason, Capitanio, Mendoza, & Amaral, 2001) found that neonatal lesions of the amygdala in monkeys lead to increased social fear and decreased fear of objects, a finding

that suggests that such lesions dissociate a system that mediates social fear from ones that mediate fear of inanimate objects. Early damage to the hippocampal formation resulted in severe memory deficits and mild changes in social behavior (Bachevalier, Alvarado, & Malkova, 1999; Beauregard, Malkova, & Bachevalier, 1995). The full syndrome required damage to both regions. Lower functioning individuals with autism are more likely to show memory impairments related to MTL functioning (Ameli, Courchesne, Lincoln, Kaufman, & Grillon, 1988; Barth et al., 1995; Boucher, 1981; Boucher & Warrington, 1976; Rumsey & Hamburger, 1988), whereas high functioning individuals with autism do not show such deficits (Barth et al., 1995). This model hypothesizes that all individuals with autism have MTL brain abnormalities but that the severity of the abnormality varies across individuals, which accounts for the heterogeneity found in the autism population.

A different version of this hypothesis (Waterhouse et al., 1996) is that less severely affected individuals have little or no dysfunction of the MTL but have significant involvement of the temporal-parietal association regions and parietal cortex, and more severely affected individuals have considerable MTL involvement, which leads to PF impairments as a consequence of faulty input from MTL structures. Thus, PF impairments are "associated" symptoms, and not specifically causal of core autistic symptoms. Studies with monkeys (Bertolino, Saunders, Mattay, Bachevalier, Frank, & Weinberger, 1997; Chlan–Fournay, Webster, Felleman, & Bachevalier, 2000; Saunders, Kolachana, Bachevalier, & Weinberger, 1998) showed that early MTL damage disrupts the development of the circuitry and functions of the PF cortex. Specifically, early MTL lesions result in delayed maturation of the dorsolateral PF cortex and dysregulation of the striatal dopaminergic system. Perhaps the impairments in PF function found in older individuals with autism (Bennetto, Pennington, & Rogers, 1996; Ozonoff, 1995; Prior & Hoffman, 1990) are secondary consequences of early MTL dysfunction. Two neuropsychological studies with 3- to 4-year-old children with ASD found no differences in PF performance for autism versus mental age–matched controls (Dawson, Munson, et al., 2002; Griffeth, Pennington, Wehner, & Rogers, 1999), whereas several studies of elementary school–age children found executive function impairments in autism relative to mental age–matched controls (e.g., Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; McEvoy, Rogers, Pennington, 1993; Pennington & Ozonoff, 1996). Executive function skills are just emerging during the early preschool period (Diamond & Goldman–Rakic, 1989), so finding a lack of syndrome-specific executive function deficits in very young children is not surprising. Autism-specific PF impairments might not become apparent until the frontal lobe is more mature, and they might be secondary to the experience-driven effects of MTL dysfunction. Recent studies have attempted to better define the executive dysfunction in older individuals with autism. Such studies suggest that older individuals with autism have particular difficulty in set shifting (Hughes, Russell, & Robbins, 1994; Ozonoff & Strayer, 1997; Ozonoff, Strayer, McMahon, & Filloux, 1994) and in performing tasks that require maintaining working memory while inhibiting prepotent responses (Roberts & Pennington, 1996; Russell, Jarrold, & Henry, 1996). There has been relatively little research on executive functioning in younger and/or more severely impaired individuals with autism, and there have been very few longitudinal studies. Such studies are important for understanding the course of PF dysfunction related to autism symptoms. Studies have shown that the siblings (Hughes et al., 1999) and the parents (Hughes, Leboyer, & Bouvard, 1997; Piven & Palmer, 1997) of individuals with autism are more impaired on executive function tasks, compared to the siblings and parents of individuals with other disabilities. Thus, executive function impairment is a candidate as a broader phenotype trait in autism.

MTL dysfunction: Relation to specific autism symptoms. Animal and human lesion studies suggest that the MTL (particularly the amygdala), is critical for social perception (Bachevalier, 2000; Baron–Cohen et al., 1999, 2000;

Dawson, 1996), including recognizing faces and facial expressions (Aggleton, 1992; Jacobson, 1986; Nelson & deHaan, 1996), forming associations between specific stimuli and their reward value (Baxter & Murray, 2000; Gaffan, 1992; Malkova, Gaffan, & Murray, 1997); recognizing the affective significance of stimuli (LeDoux, 1987); perceiving body movements, including gaze direction (Brothers et al., 1990); and for certain cognitive abilities that are likely to be important for social perception and imitation, such as cross-modal association (Murray & Mishkin, 1985). Evidence supports the continued investigation of the amygdala's role in symptom expression in autism (Baron–Cohen et al., 2000).

Less attention has been paid to the potential consequence of hippocampal dysfunction and its relation to specific autism symptoms. The hippocampal system (hippocampus, parahippocampus, entorhinal cortex, and perirhinal cortex) is important for memory functions including feature binding, memory for context, source memory, and deferred imitation. Such memory skills are integral to forming representations of social events. Cohen and Eichenbaum (1993; for a review, see Cohen, Ryan, Hunt, Romine, Wszalek, & Nash, 1999) proposed that the hippocampal system is involved in the binding of items or events into a cohesive memory. For example, the hippocampal system becomes active when encoding a novel scene (Stern, Corkin, Gonzalez, Guimaraes, Baker, Jennings, Carr, Sugiura, Vedantham, & Rosen, 1996), recalling semantically encoded words (Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996) and scenes (Montaldi, Mayes, Barnes, Pirie, Hadley, Patterson, & Wyper, 1998), and forming faces–name associations (Kapur, Friston, Young, Frith, & Frackowiak, 1995) and associations between items (Henke, Buck, Weber, & Weiser, 1997). Increased relational or associative memory is correlated with increased activation of the hippocampal system (e.g., Henke et al., 1997; Montaldi et al., 1998).

An impairment in feature binding, which involves the hippocampal–PF circuit (e.g., Mitchell, Johnson, Raye & D'Esposito, 2000), might explain some of the cognitive impairments exhibited by individuals with autism. Frith (1989) described a cognitive profile in autism characterized by a failure to integrate information into a meaningful whole. On a number of tasks assessing "central coherence" (Frith, 1989), individuals with autism fail to perceive the Gestalt and prefer parts on embedded figures, block design, and drawing tasks (Mottron, Belleville, & Menard, 1999; Shah & Frith, 1993). Parents of children with autism also demonstrate a similar bias toward part-based processing (Happe, Briskman, & Frith, 2001). This inability to bind features into a coherent whole might also be manifest in difficulties in face processing (see discussion below) and/or a failure to bind items into a coherent sequence or event.

Little is known about context memory in individuals with autism. If impaired, it might help explain the difficulty in stimulus generalization shown by most individuals with autism (Fein, Tinder, & Waterhouse, 1979; Lovaas, Koegel, & Schreibman, 1979). Impairments in context memory might result in each part being stored as an individual representation, rather than a coherent whole. This could contribute to the extraction of nonsalient features from an event, a lack of understanding of the context of the event, and a failure to generalize the event to another similar event. As a consequence, individuals with autism might show superior source memory (Bennetto, Pennington, & Rogers, 1996) and be less susceptible to false memories (Beversdorf, Smith, Crucian, Anderson, Keillor, Barrett, Hughes, Felopulos, Bauman, Nadeau, & Heilman, 2000) because their memories are influenced less by related events. In typical individuals, the Gestalt or meaning of the event is more important than the individual details of that event; this leads to the ability to abstract the salient features from the event and apply them to similar situations. However, if the parts were more important than the whole, any shift or change in the parts would result in either disorganized or deficient recall for the whole event. It would be difficult to abstract a schema from multiple exposures to similar events.

Another important memory function mediated by the MTL is deferred imitation and memory for event sequences, which have been shown to be impaired in children with autism

(Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998a). Dawson and colleagues (1998) found that deferred imitation ability was highly correlated with performance on a MTL task, DNMS. Those children with autism who performed fewer imitative acts on the immediate and deferred imitation tasks needed more trials to reach criterion on the DNMS and had more severe autistic symptoms (e.g., joint attention). Similarly, McDonough, Mandler, McKee, and Squire (1995) found that patients with MTL damage, but not frontal damage, reproduced fewer actions and action sequences on a deferred imitation task.

MTL dysfunction might be a core deficit in autism, or it might be a secondary or associative dysfunction. Saitoh, Karns, and Courchesne (2001) recently demonstrated that individuals with autism have smaller dentate regions (a component of the hippocampal circuitry), with the largest deviations from normal occurring in young autistic children (between 2.9 and 4 years). The human dentate is one of the last regions to complete neurogenesis (Bayer, Altman, Russo, & Zhang, 1993), the region still showing immaturity at 15 months of age (Seress, 1992). The dentate may continue to experience neurogenesis throughout adult life, and there are increases in neuron production resulting from exposure to enriched environments (Kempermann, Juhn, & Gage, 1997) and reductions resulting from exposure to social stresses (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998; Sapolsky, 2000). Saitoh and colleagues (2000) hypothesize that delayed neurogenesis and maturity of the dentate might "derail" the formation of connections between hippocampal areas, and thus lead to early memory disorders. This suggests an important role for intervention, as it is possible that this system might show a high degree of early plasticity.

It is also possible that an insult during pregnancy or birth might lead to a cascade of events that result in MTL dysfunction. Obstetric complications have been associated with a range of childhood developmental disorders (e.g., Eaton, Mortensen, Thomsen, & Frydenberg, 2001), including autism (Bolton, Murphy, Macdonald, Whitlock, Pickles, & Ritter, 1997; Juul–Dam, Townsend, & Courchesne, 2001; Pickles, Starr, Kazak, Bolton, Papanikolaou, Bailey, Goodman, & Rutter, 2000). Complications, such as hypoxic–ischemic insults, placental insufficiency, and prenatal stress, have been shown to have a disproportionate effect on the development of the hippocampal system (e.g., Gadian, Aicardi, Watkins, Porter, Mishkin, & Vargh–Khadem, 2000; Rees, Mallared, Breen, Stringer, Cock, & Harding, 1998; Stefanis, Frangou, Yakeley, Sharma, O'Connell, Morgan, Sigmundsson, Taylor, & Murray, 1999). For example, the earlier onset of schizophrenia symptoms is associated with a reduction of hippocampal volume but only in those patients with a history of severe birth complications (Stefanis et al., 1999). In addition, the smaller the hippocampal volume, the earlier will be the onset of schizophrenia symptoms. It is unknown whether a correlation exists between hippocampal damage and birth complications in autism. It is possible that obstetric abnormalities are a consequence of the abnormality of the fetus rather than an independent contributor to the disorder (Bolton et al., 1997). Thus, MTL dysfunction in autism might be related to (a) an independent, inherited genetic risk factor for hippocampal dysfunction, (b) a risk factor that results in obstetric complications that might contribute to hippocampal damage, or (c) disordered early input that leads to MTL dysfunction.

Temporal lobe and its role in face processing

There is increasing interest in investigating the potential role of the brain regions that are specialized for face processing in autism. Some investigators have theorized that aspects of face processing are critical to the development of social relationships and theory of mind (Baron–Cohen, 1995; Brothers, 1990; Cole, 1998; Perrett, Harries, Mistlin, & Hietanen, 1990; Perrett, Hietanen, Oram, & Benson, 1992; Williams et al., 2001). Humans and other primates derive valuable information about the actions and intentions of others by interpreting information from the face, such as direction of gaze and facial gestures and expressions of emotion. Animal, human brain damage, event-related potential (ERP)

and fMRI studies have provided detailed information about the cognitive neuroscience of face processing. We next review the studies on the cognitive neuroscience of face processing and then discuss what is known about abnormal face processing in autism.

Neural bases of face processing: Primate and human brain damage studies. We know a great deal about neural systems that subserve face processing in adult humans and primates, although controversy still exists regarding whether specific neural systems exist that are specialized for faces per se (Gauthier & Logothetis, 2000). Monkeys have face-selective cells in the inferior temporal areas TEa and TEm, the superior temporal sensory area, the amygdala, the ventral striatum (which receives input from the amygdala), and the inferior convexity (Baylis, Rolls, & Leonard, 1987; Desimone, Albright, Gross, & Bruce, 1984; Rolls, 1992; O Scalaidhe, Wilson, & Goldman–Rakic, 1997; Williams, Rolls, Leonard, & Stern, 1993; Wilson, O Scalaidhe, & Goldman–Rakic, 1993). Primates have cells in a region of the STS that respond to facial gestures and direction of gaze (Perrett et al., 1992; Perrett, Smith, Mistlin, Chitty, Head, Potter, Broennimann, Milner, & Jeeves, 1985; Yamane, Kayi, & Kawano, 1988). Perrett et al. (1990) and others have suggested that this region, along with the amygdala and orbitofrontal cortex, may form part of a neural system involved in social attention, social bonding, and the use of facial gestures (Brothers & Ring, 1993; Kling & Steklis, 1976; Perrett et al., 1990, 1992). Such a system may also exist in humans (Baron–Cohen, 1995; Brothers, 1996); regions of the human temporal cortex may be homologous to monkey STS.

Studies of patients with neurological damage also provide information regarding the specific brain regions involved in face processing. The selective impairment of face recognition (termed "prosopagnosia" by Bodamer in 1947) has been observed in patients with damage to the occipitotemporal regions (e.g., Damasio et al., 1990), and there is evidence that the right hemisphere plays a more crucial role than the left (Sergent & Signoret, 1992b). Damage to the amygdala also impairs face recognition (Aggleton, 1992; Damasio, Damasio, & Van Hoesen, 1982). Electrical stimulation studies in presurgical epileptic patients have demonstrated that single neurons in medial temporal structures mediate the discrimination of faces from inanimate objects (Fried, MacDonald, & Wilson, 1997). Other neurons in the same region were found to respond differentially to novel versus familiar faces during a recognition task.

Early stage processing of static faces: ERP and fMRI studies. The amplitude and latency of the ERP have been used to index and differentiate the allocation of resources and the temporal characteristics of information processing. Many ERP studies have revealed a face-specific component, peaking at approximately 170 ms after stimulus onset, that is related to the early stage processing of faces (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Botzel, Schulze, & Stodieck, 1995; Eimer, 1998, 2000; George, Evans, Fiori, Davidoff, & Renault, 1996). This N170 component is typically more negative at right versus left posterior temporal loci and may be positive at frontocentral cites. This component is smaller or absent to nonface categories of stimuli (e.g., furniture) and to animal faces (Bentin et al., 1996).

Several studies have begun to elucidate the specificity of the early face processing components. Bentin et al. (1996) found that N170 latency is shorter for upright faces (173 ms) than for inverted faces (182 ms), eyes (186 ms), or noses and lips (210 ms). Similarly, Eimer (1998) found a small but highly consistent delay in N170 in response to faces without eyes and eyebrows. These results suggest that the timing of the processes indexed by the N170 is affected (i.e., becomes slower) when the configuration or orientation of the face components is altered. Inverted faces interfere with the brain's special ability to rapidly recognize the configuration or Gestalt of a face and instead elicit the processing of individual features. Furthermore, these ERP results suggest that the structural encoder is sensitive to the presence of salient face characteristics, especially the eyes. Studies utilizing intracranial electrodes also found the am-

plitude of the face-specific ERP component to be greatest in response to the eyes, then the mouth, and then the nose (Allison, Puce, Spencer, & McCarthy, 1999; McCarthy, Puce, Belger, & Allison, 1999; Puce, Allison, & McCarthy, 1999).

Although the voltage distribution of the ERP responses to faces and eyes (but not lips or noses) is consistent with an occipitotemporal sulcus generator, this component has not yet been specifically modeled. Using magnetoencephalography (MEG), Watanabe and colleagues (Watanabe, Kakigi, Koyama, & Krino, 1999) found that responses to faces with open or closed eyes were of shorter latency than eyes alone for the 1M component (approx. 130 vs. 145 ms, respectively) and 2M component (approx. 183 vs. 209 ms, respectively). Dipole modeling of the MEG responses suggests sources located in the right and left primary visual cortex as well as the right inferior temporal cortex. This three-dipole model accounts for both the face stimuli as well as eyes alone but does not fit responses to hands or scrambled faces. These results suggest that the neural generators for whole face processing and eye processing may be colocated, but that individual face parts (e.g., eyes, nose, mouth) require additional processing time. Taken together, the encoding of whole faces and eyes alone may evoke a qualitatively different process than those related to perceptually similar stimuli (e.g., scrambled faces, inverted faces, etc.).

By using more spatially sensitive neuroimaging methods (e.g., PET and fMRI), studies demonstrated a focal region within the anterior ventral occipitotemporal cortex (termed the *fusiform face area* or FFA, which is contained in but does not fill Brodmann areas 18, 19, and 37). This responds in a highly selective fashion to faces, compared to a wide variety of nonface visual stimuli. PET studies demonstrated increased cerebral blood flow in the fusiform gyrus (and nearby occipitotemporal cortex) during no-delay match to sample tasks with face stimuli (Haxby, Horwitz, Ungerleider, Maisog, Pietrini, & Grady, 1994) and during a face identification task (Sergent, Ohta, & MacDonald, 1992). Replicating the Haxby et al. (1994) PET study with fMRI, Clark and colleagues (Clark, Keil, Maisog, Courtney, Ungerleider, & Haxby, 1996) were able to more specifically localize the effect to a ribbon of cortex approximately 1 cm wide, extending from the ventrolateral occipital cortex in the inferior occipital sulcus to the ventral occipitotemporal cortex in the fusiform gyrus and lateral occipitotemporal sulcus. Other fMRI studies were able to demonstrate the same effects in the FFA during the passive viewing of faces in comparison with several types of control stimuli, including nonface objects, a scrambled face, or inverted face stimuli (e.g., Haxby, Ungerleider, Clark, Schouten, Hoffman, & Martin, 1999; Hoffman & Haxby, 2000; Kanwisher, McDermott, & Chun, 1997; Kanwisher, Tong, & Nakayama, 1998; McCarthy, Puce, Gore, & Allison, 1997; Puce, Allison, Asgari, Gore, & McCarthy, 1996; Puce, Allison, Gore, & McCarthy, 1995; Wojciulik, Kanwisher, & Driver, 1998). Kanwisher et al. (1997) conducted an elaborate series of studies designed to test the specificity of activation of the FFA by human faces, and they argued that FFA activation cannot be explained by alternative features of the face viewing task (e.g., visual attention, subordinate-level classification, or general processing of any animate or human forms).

Although there is strong evidence that the FFA is involved in processing face stimuli, several studies suggest that the fusiform is also involved in the processing of any stimuli with which the viewer has particular familiarity or expertise. For example, Gauthier and colleagues (Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999) demonstrated that the acquisition of expertise with novel objects ("greebles") led to increased activation in the right hemisphere face areas for matching of upright greebles as compared to matching inverted greebles. The same areas were also more activated in experts than in novices during the passive viewing of greebles. Thus, expertise seems to be one factor that leads to specialization in the face area. There have, however, been case reports of individuals who lose the ability to recognize faces without losing the ability to recognize individual examples of other stimuli for which they have expertise (Sergent & Signoret, 1992a). Thus,

there may be pathways within the fusiform that are specific to faces, even if the region can be activated by other stimuli for which the viewer has expertise.

Processing of face movements: ERP and fMRI studies. Given the well-documented core impairments in joint attention in autism, an understanding of brain abnormalities related to a failure to detect another person's eye gaze patterns is extremely relevant to our understanding of autism. The N170 is sensitive to such face movements. Using ERP, Puce, Smith, and Allison (2000) reported significantly larger and faster N170s over the bilateral temporal scalp when participants viewed averting eyes and opening mouths relative to eyes gazing back toward the observer and mouths closing. The bilateral temporal N170s could be a neural response to specific aspects of "biological motion" that are interpreted as socially important. The direction of gaze is important as a social cue and in communication between individuals, and it also offers critical information about another's direction of attention and intention (Taylor, Itier, Allison, & Edmonds, 2001). Participants in the Puce et al. (2000) experiment noted that the *averting* eyes stimulus elicited an urge to follow the eye gaze and the *opening* mouth stimulus was associated with the anticipation of speech.

The fMRI studies demonstrated that regions surrounding the STS are involved in processing face movements and in the perception of gaze direction. In a study comparing the passive viewing of moving eyes and mouths to a checkerboard pattern in which comparable target areas moved, Puce, Allison, Bentin, Gore, and McCarthy (1998) found that only the moving eyes and mouths activated the posterior STS. Hoffman, Phillips, and Haxby (2001) found that the STS was activated equally by fast dynamic changes in face identity (i.e., a face "morphing" into another face) as by fast dynamic changes in gaze direction, suggesting that face movement in general, and not just eye and mouth movement, activates the STS.

Other investigators have used static photos of faces with a direct or averted gaze to examine the role of the STS in gaze perception. In a study by Hoffman and Haxby (2000), participants were asked to attend to the identity of either faces or eye gaze. The results indicated that eye-gaze perception was mediated by the STS, with additional recruitment of the intraparietal sulcus to track the direction of gaze and to focus attention in that direction. In addition, both the left STS and bilateral intraparietal sulcus activated more strongly to passive viewing of faces with direct gaze than with averted gaze. George, Driver, and Dolan (2001) found greater activation around the fusiform gyrus when participants viewed faces with direct gaze, in comparison with averted gaze, regardless of head orientation. Moreover, direct gaze led to a greater correlation between activity in the fusiform and the amygdala, a region associated with emotional responses and stimulus saliency. By contrast, faces with averted gaze (again, regardless of head orientation) yielded increased correlation between activity in the fusiform and the intraparietal sulcus, a region associated with shifting attention to the periphery.

The cerebellum may also be involved in the perception of gaze direction. Dubaeau, Iacobini, Koski, and Mazziotta (2001) found activation in the right cerebellum, just inferior to the FFA, in a task in which participants were asked to indicate whether eye gaze was to the right or left, in comparison to a task in which they indicated whether two arrows were pointing to the right or left. They concluded that cerebellar activity reflects joint attention mechanisms (see also Akshoomoff et al., 2002). In summary, fMRI studies suggest that the fusiform gyrus, STS, intraparietal sulcus, and possibly the cerebellum may be involved in perceiving gaze direction and shifting attention to the direction of the gaze.

Evidence for abnormal face processing in autism: A developmental perspective. Neural systems that mediate face processing exist very early in life; hence the impairment of face processing may be one of the earliest indicators of abnormal brain development in autism. In TD infants, the face holds particular significance and provides a range of nonverbal information that is important for communication and survival (Darwin, 1872/1965). A visual preference for faces (Goren, Sarty, &

Wu, 1975) and very rapid face recognition (Walton & Bower, 1993) are present at birth. By 6 months, infants show differential ERPs to familiar versus unfamiliar faces (de Haan & Nelson, 1997, 1999). Infants also can discriminate among and categorize at least some facial expressions early in life (Nelson, 1993). In summary, humans have neural systems devoted to face processing and they begin functioning very early in life.

The profound disability in social cognition found in autism may be initially evident in a failure to attend to people's faces, and this abnormality is presumed to reflect abnormal neural representation of this process in the brain. In a study of home videotapes of first birthday parties, failure to attend to others' faces was the single best discriminator between 1-year-olds later diagnosed with autism versus those with typical development (Osterling & Dawson, 1994). Several studies of children, adolescents, and adults with autism showed impairments in both face matching and recognition (Boucher & Lewis, 1992; Boucher, Lewis, & Collis, 1998; Cipolotti, Robinson, Blair, & Frith, 1999; Hauck, Fein, Maltby, Waterhouse, & Feinstein, 1998; Jambaque, Mottron, Ponsot, & Chiron, 1998; Klin et al., 1999; Ozonoff, Pennington, & Rogers, 1990; Tantam, Monaghan, Nicholson, & Stirling, 1989; Teunisse & DeGelder, 1994). Hobson et al. (1988a) and Langdell (1978) examined whether older individuals with autism show the "face-inversion effect" seen in control subjects, that is, a greater decrement in memory for inverted versus upright faces, as compared with inverted versus upright nonface visual stimuli. In both studies, individuals with autism recognized inverted faces *better* than did control subjects: this suggests that individuals with autism are not using the normal configural approach for processing upright faces. Two recent fMRI studies of high-functioning individuals with autism and Asperger syndrome showed a failure to activate the FFA during face processing (Pierce, Muller, Ampbrose, Allen, & Courchesne, 2001; Schultz, Gauthier, Klin, Fulbright, Anderson, Volkmar, Skudlarski, Lacadie, Cohen, & Gore, 2000). In another fMRI study, Baron–Cohen and colleagues (Baron–Cohen et al., 1999) evaluated both individuals with high-functioning autism or Asperger syndrome and normal controls while they made judgments based on the expressions of another person's eyes regarding what the other person might be thinking or feeling. In normal individuals, they found increased activation in the superior temporal gyrus, amygdala, and parts of the PF cortex. Individuals with autism or AS activated the frontotemporal regions, but not the amygdala, when making inferences from the eyes.

Dawson and colleagues (Dawson, Carver, et al., 2002; McPartland, Dawson, Carver, & Panagiotides, 2001a, 2001b) recently conducted two electrophysiological studies of face processing in individuals with autism. In the first study, 3- to 4-year-old children with ASD, DD, or typical development were presented with images of the mother's versus a stranger's face and of their favorite versus an unfamiliar toy. Typical and DD children showed differential ERP responses to the mother's versus stranger's face and to a favorite versus an unfamiliar object. In contrast, children with autism failed to show a differential brain electrical response to the mother versus stranger, but did show greater ERP to the unfamiliar versus favorite object. Their ERP patterns in response to objects were quite similar to those of the chronological age–matched typical children (i.e., greater P400 and Nc amplitude at the lateral scalp locations in response to the unfamiliar object).

In a second ERP study, McPartland and colleagues found that high functioning adolescents and adults with autism exhibited longer latency of the face-specific N170 ERP component relative to IQ-matched normal adolescents and adults, did not show a differential ERP response to upright versus inverted faces, and did not show the normal right-lateralized ERP consistently found in normal individuals (McPartland et al., 2001a, 2001b). This suggests that, in autism, the neural system related to face processing is less efficient (slower), lacks specificity to faces, and may be abnormally represented in the brain.

Are abnormalities in face processing related to faulty face encoding or secondary to ab-

normalities in social attention? It is possible that the face processing impairments in autism represent innate abnormalities in early stage face processing (i.e., a faulty "starter set" for structural face encoding). Alternatively, such impairments might be caused by abnormal *development* of the neural system that mediates face processing related to a failure to pay attention to faces (i.e., faulty input or experience). Beginning early in life for individuals with autism, there may be a deprivation of critical experience-driven input that results from a failure to pay normal attention to faces, particularly the eye region. Dawson and others (Dawson, Osterling, Rinaldi, Carver, & McPartland, 2001; Mundy & Neal, 2000) hypothesized that abnormal social attention or "social orienting" in autism is related to a lack of sensitivity to social reward. More broadly, this lack of sensitivity to social reward is manifested in impaired social affiliation, as reflected in a lack of interest in others or in forming friendships. Here, we are interested in how such an impairment in social affiliation or social reward might be reflected in attentional abnormalities specific to face processing.

Human and nonhuman primates normally pay a lot of attention to faces, especially the eyes. Behavioral studies suggest that the most salient parts of the face are, in order of importance, the eyes, mouth, and nose (reviewed in Shepherd, 1981). Studies utilizing intracranial ERPs to face stimuli have demonstrated that the amplitude of the face-specific ERP component decreases in the same order (Allison et al., 1999; McCarthy et al., 1999; Puce et al., 1999). Eye-scanning studies in humans (Yarbus, 1967) and monkeys (Nahm, Perret, Amaral, & Albright, 1997) show that the eyes and hair or forehead are scanned more frequently than the nose. Human infants focus on the eyes rather than the mouth (Haith, Bergman, & Moore, 1979). With respect to studies of autism, such studies have demonstrated that 9- to 10-year-old children with autism perform better on face matching tasks when matching is contingent on the lower face or mouth as opposed to the upper face or eyes (Joseph, 2001; Langdell, 1978). Using eye-tracking technology to measure visual fixations, Klin, Jones, Schultz, Volkmar, and Cohen (2002) recently reported that, when viewing naturalistic social scenes, adults with autism show abnormal patterns of attention characterized by greatly reduced attention to eyes and increased attention to mouths, bodies, and objects. Thus, it appears that autism is associated with abnormal attention to the face, especially the eye region.

How might such faulty attentional mechanisms affect the development of face processing? Morton and Johnson (1991) hypothesize that early face processing abilities are served by a subcortical neural system, which is replaced by a less fragile and experience-dependent cortical system that emerges by 6 months of age. These changes in the face-processing system may reflect "experience expectant developments" (Nelson, 2001), meaning that they involve a readiness of the brain to receive specific types of information from the environment (Greenough, Black, & Wallace, 1987). This readiness occurs during sensitive periods, during which specific types of information are reliably present for most individuals. Exposure to faces is a reliable experience for most human infants and likely facilitates the development of a neural system specialized for faces. Nelson (1993) found human infants superior to adults in discriminating monkey faces, suggesting that experience with human faces results in a "perceptual narrowing" similar to what is observed with speech perception (Doupe & Kuhl, 1999). Gauthier et al. (1999) showed that increased expertise in object recognition is associated with increased activation of the fusiform gyrus, a region typically activated by face processing. These studies suggest that specialization of the fusiform gyrus is influenced by both experience and expertise.

Experience may also play a role in abnormal development of the face-processing system in autism (Carver & Dawson, in press). It is possible that the abnormalities in face processing found in autism may be related to abnormalities in social attention and, more specifically, that reward mechanisms that naturally draw the TD infant's attention to the eyes are dysfunctional in autism. Such reward mechanisms normally facilitate mutual gaze and the

acquisition of knowledge about other people's intentions and facial expressions (Blass, 1999). Representations regarding the anticipated reward value of a stimulus begin to motivate and direct attention by the second half of the first year of life (Ruff & Rothbart, 1996). Establishing such representations regarding the anticipated reward value for *social stimuli* may be challenging for children with autism because social reward feedback (e.g., a smile in response to a behavior) is less predictable and more variable compared to nonsocial reward feedback (e.g., a sound in response to pushing a button; Dawson & Lewy, 1989). Gergely and Watson (1999) showed that, in contrast to TD infants and toddlers, children with autism show a strong preference for highly contingent, nonvariable (i.e., perfect rather than imperfect) contingency feedback. The normal infant's attention is drawn to the imperfect contingent feedback that is characteristic of social interactions, whereas the child with autism is drawn to the less variable feedback of nonsocial stimuli (Gergely & Watson, 1999; Dawson & Lewy, 1989). This might result in a lack of attention to social stimuli, including faces, thereby creating a kind of deprivation of normal learning experiences with faces.

Alternatively, if the abnormality is in the "starter set" (i.e., the structural encoding of faces), although children with autism may be responsive to certain types of social reward (e.g., tickling, hugging, rough and tumble play), reward values would not be associated with faces because faces are not encoded properly and/or efficiently, if at all. Either way, the failure to associate the encoding of aspects of the face with reward likely would affect the consolidation of memories for faces, facial gestures (e.g., eye gaze movements), and facial expression. The amygdala is involved in assessing the emotional significance (reward value) of a stimulus (Gaffan, 1992; Malkova et al., 1997). There is increasing evidence that the amygdala plays a role in enhancing the memory for emotional stimuli. The physiological arousal experienced in association with emotional events or stimuli may be an important component in an amygdala-based memory system (Phelps & Anderson, 1997). Patients with amygdala damage do not show typical differential forgetting curves for arousing and nonarousing stimuli (i.e., they do not show enhanced recall for arousing stimuli). These patients have been shown to have intact recall for words that were emotional in meaning, but not arousing as measured by skin conductance response (Phelps, LaBar, & Spencer, 1997). If there exists amygdala dysfunction in autism, this might contribute to an impairment in memory consolidation for faces, gaze patterns, and facial expressions.

There are implications of these alternatives for clinical intervention with young children with autism (Carver & Dawson, in press). If children with autism fail to develop a normal face processing ability because they lack critical experience with faces, then intervention should focus on motivating children with autism to look at and take an interest in faces by making faces rewarding to them. This is, in fact, the approach taken by most early behavioral interventions for children with autism. Children are explicitly trained by the examiner to "Look at me" and then rewarded for doing so. Even if the problem for children with autism is not in their motivation to attend to faces but rather a difference in the starter set, changing the environmental input by training them to become face experts may provide important stimulation to this neural system that might have a remedial effect. If children with autism have a fundamental impairment in the face processing neural system that is unresponsive to intervention, then the focus of intervention should be in helping them to develop compensatory strategies for processing and remembering faces. Face processing, which includes sensitivity to eye gaze pattern and facial expressions of emotion, is fundamental to early social cognition and an impairment in this domain would be expected to affect the development of joint attention, social referencing, and responses to emotional cues. Thus, early intervention in this domain is important.

Brain regions involved in motor imitation

Several groups suggested that impairments in motor imitation might be central to the autism

syndrome (Dawson & Adams, 1984; Dawson & Lewy, 1989; DeMyer, Alpern, Barton, DeMyer, Chuchill, Hingtgen, Bryson, Pontius, & Kimberlin, 1972; Meltzoff & Gopnik, 1993; Rogers & Pennington, 1991; Williams et al., 2001). Imitation impairments in autism are well documented (see Smith & Bryson, 1994, and Rogers, 1999, for reviews). Such impairments extend beyond face movements to include gestures and actions with objects (Rogers, Bennetto, McEvoy, & Pennington, 1996), suggesting that imitation impairments are not fully explained by face processing impairments (although face processing impairments would be expected to impact the imitation of facial expressions and affect). Meltzoff and Gopnik (1993) proposed that imitation is a key starting state for the development of theory of mind. They argue that the ability to match the seen behavior of others with the same behavior performed by the self is critical for recognizing the linkage between the emotional and mental experiences of the self and others.

Several brain regions have been identified as important for imitative behavior. Patients with left frontal lesions exhibit dyspraxia (Goldenberg, 1995; Goldenberg & Hagman, 1997; Merians, Clark, Poizner, Macauley, Gonzalez–Rothi, & Heilman, 1997), and electroencephalogram studies have shown that the left hemisphere is activated during the imitation of hand and facial movements (Dawson, Warrenburg, & Fuller, 1985). Animal studies have demonstrated that cells in the STS code the posture or movements of the face, limbs, or whole body (Oram & Perrett, 1994; Perrett et al., 1985; Perrett, Harries, Bevan, Thomas, Benson, Mistlin, Chitty, Hietanen, & Ortega, 1989; Perrett, Smith, Potter, Mistlin, Head, Milner, & Jeeves, 1984).

Action-coding neurons have been identified in the PF cortex (area F5) in monkeys (Gallese, Faddiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Matelli, Bettinardi, Paulesu, Perani, & Fazio, 1996). These neurons, called *mirror neurons,* fire when a monkey either performs or views another monkey performing specific actions. Functional imaging studies have demonstrated that viewing and imitating hand movements activates the parietal and PF regions (premotor cortex and Broca's area; Grafton, Arbib, Fagdiga, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). Based on a functional imaging study, Decety et al. (2002) recently reported that imitation activated the superior temporal gyrus and that, moreover, the left inferior parietal cortex was activated when people imitated the action of others whereas the right inferior parietal cortex was activated when another person imitated their actions. The fact that parts of the superior temporal lobe are involved in the perception of faces, faces gestures, and eye movements, as well as imitative behavior, suggests that it might be a region of core brain dysfunction in autism.

In summary, several brain regions play a key role in aspects of social behavior known to be impaired in autism, including impairments in joint attention, face processing, and motor imitation. These brain regions include the MTL (amygdala, hippocampus, and entorhinal cortex), the PF cortex (ventromedial, Broca's area), parts of the temporal lobe (fusiform gyrus, STS), and the inferior parietal cortex. Such behaviors and associated brain regions may be informative for developing quantitative measures of the autism broader phenotype.

Nature and genetic bases of language impairment in autism

A second domain of impairment in autism pertains to communication and language. During the past decade, most research on language impairment in autism has focused on the pragmatic deficits (Lord & Paul, 1997; Loveland, Landry, Hughes, Hall, & McEvoy, 1988; Loveland & Tunali, 1993; Tager–Flusberg, 1996, 1999; Tager–Flusberg & Sullivan, 1995; Wetherby, 1986; Wilkinson, 1998). However, these communicative impairments may be secondary to deficits in theory of mind and other aspects of social impairment (Capps, Kehres, & Sigman, 1998; Tager–Flusberg, 1993, 1996; Tager–Flusberg & Sullivan, 1995).

Whereas pragmatic impairments are universal in autism, the degree of impairment in other aspects of language, such as vocabulary and grammar, is highly variable. Some indi-

viduals show normal functioning in these domains, whereas others have severe impairments (Lord & Paul, 1997). Kjelgaard and Tager–Flusberg (submitted) recently argued that the variability found in these aspects of language ability reflects an overlap between autism and specific language impairment (SLI), and that this has implications for genetic studies of autism. SLI itself is heterogeneous, but it is generally defined as having a nonverbal IQ within the normal range and performance on tests of vocabulary and/or grammatical ability 1 *SD* below the mean. Individuals with SLI have been shown to have specific difficulties on the nonword repetition test, which assesses phonological processing (Bishop, North, & Donlan, 1996; Dollaghan & Campbell, 1998; Gathercole & Baddeley, 1990). Children with SLI have been shown to have volumetric and asymmetry differences from normal in the planum temporale and parietal and frontal cortex and alterations in the magnocellular neurons in the lateral geniculate nucleus and medial geniculate nucleus (see Tallal & Benasich, 2002). PET studies of phonological processing have yielded variable results, but the brain regions most that are consistently activated include Broca's area (Demonet, Chollet, Ramsay, Cardebat, Nespoulous, Wise, Rascol, & Frackowiak, 1992; Paulescu, Frith, & Frackowiak, 1993; Zatorre, Evans, Meyer, & Gjedde, 1992), the secondary auditory cortex (Demonet et al., 1992; Paulescue et al., 1993), and the supramarginal gyrus (Paulecsu et al., 1993; Petersen, Fox, Posner, Mintun, & Raichle, 1989; Zatorre et al., 1992).

In a relatively large study of language function in children with autism (N = 89), Kjelgaard and Tager–Flusberg (submitted) found that approximately 25% of the sample had essentially normal vocabulary and grammatical ability. Furthermore, they found that speaking children with low vocabulary and grammar skills had spared articulation skills but were impaired on a nonsense word repetition test. Thus, their language profile paralleled that found in children with SLI (Bishop et al., 1996; Dollaghan & Campbell, 1998; Gathercole & Baddeley, 1990). In fact, this pattern of deficits has been viewed as defining the phenotype of SLI (Tager–Flusberg & Cooper, 1999). They note that, unlike echolalia, the nonsense word repetitive test does not depend on rote memory, but instead it requires the child to analyze the acoustic and phonetic properties of the speech stream to derive the phonological representation and to hold the representation of the segments in working memory in order to reproduce them in a motor program. Again, this pattern is similar to children with SLI: even when they have good articulation skills, these children show systematic difficulties on tests of nonword repetition.

Coffey–Corina and Kuhl (2001) also found evidence for basic phonological processing impairment in autism. They studied speech processing in young children with ASD using an electrophysiological mismatch negativity paradigm. Three- to four-year-old children with ASD and age-matched children with typical development watched a video of their choice while passively listening to two different speech sounds: one syllable, /wa/, was presented on 85% of the trials (standard), and a different syllable, /ba/, was presented the remaining 15% of the trials (deviant). The TD children showed a significant EEG difference between standards and deviants, whereas children with ASD showed no significant EEG differences for these speech stimuli. The results suggest that basic auditory–linguistic processing may be fundamentally different in some children with autism.

Kjelgaard and Tager–Flusberg (submitted) argue that their study is evidence for significant overlap between autism and SLI. They note that autism and SLI are both complex genetic disorders with high heritability (Santangelo & Folstein, 1999; Tallal & Benasich, 2002; Tomblin & Zhang, 1999). Both disorders involve several genes, and family studies have identified a broader phenotype. There are elevated rates of language-related deficits in family members of individuals with autism, including delayed onset of language and language-related learning deficits (Bolton et al., 1994; Fombonne, Bolton, Prior, Jordan, & Rutter, 1997; Piven & Palmer, 1997). Furthermore, Hafeman, and Tomblin (1999) found a significantly elevated risk of autism among siblings of SLI probands. Linkage to the same

region on chromosome 7 has been found for both disorders (Fisher, Vargha–Khadem, Watkins, Monaco, & Pembrey, 1998; International Molecular Genetic Study of Autism Consortium, 1998). In conclusion, it is likely that there exist shared genetic and phenotypic characteristics among families with SLI and autism. Separating aspects of language that reflect the core communicative impairments found universally in autism from those aspects characteristic of SLI that show up in only a subgroup of children may be useful in defining the genetic phenotype of autism.

Conclusion

Progress in understanding the cause, nature, and treatment of autism will require an integration of concepts, approaches, and empirical findings from genetic, cognitive neuroscience, animal, and clinical studies. The need for such integration has been a fundamental tenet of the discipline of developmental psychopathology from its inception (Cicchetti, 1984, 1990). Definitions of the broader phenotype of autism based on knowledge of the cognitive neuroscience of social and language ability will help define meaningful subcomponents of complex systems that underlie social and language behavior. Fortunately, the cognitive neurosciences of social behavior and language are rapidly growing fields, and autism researchers will continue to reap the benefits of this growth. Similarly, scientists seeking to illuminate normal developmental processes and gene–behavior relations will benefit from the study of individuals with autism. Research on pathology allows researchers to confirm and expand on the developmental principles on which their theories were founded (Cicchetti, 1984, 1990, 1993). For example, by studying the impact of early interventions on brain and behavioral functioning in young children with autism, scientists will learn about the development and plasticity of the neural systems mediating face processing, imitation, and language, among others. The discovery of autism susceptibility genes will allow us to understand the genetic bases of social and language abilities and help explain normal variability in the phenotypic expression of these abilities.

Table 1 and Figure 2 provide an overview of the concepts discussed in this article, illustrating candidate autism broader phenotype measures for QTL studies, their associated brain regions, and possible measures. Six candidate traits are proposed: (a) face processing, which includes the structural encoding of facial features and face movements, such as eye gaze, (b) social affiliation or sensitivity to social reward, which pertains to the social motivational impairments apparent in many individuals with autism, (c) motor imitation ability, particularly the imitation of body actions, (d) memory, specifically those aspects of memory that are mediated by the MTL–PF circuits, such as feature binding, (e) executive function, especially planning and flexibility, and (f) language ability, particularly those aspects of language that overlap with SLI, namely, phonological processing. Translating these concepts into empirically sound dimensional measures that can be used with affected and nonaffected individuals of different ages and abilities will be a tremendous challenge, and there is no guarantee that such measures will be linked to specific genes.

The discovery of autism susceptibility genes will likely have a significant impact on our understanding of autism and how to improve clinical intervention. For example, as genes are discovered and animal models are developed, we will gain a better understanding of how early symptoms of autism manifest themselves and unfold over time and how early damage to one brain system affects the development of later emerging ones. It may eventually be possible to identify infants at risk for autism based on the presence of susceptibility genes. The increased surveillance of such infants could be accompanied by attempts at very early intervention. As it is possible that some of the symptoms we now define as autism are caused or exacerbated by the lack of specific environmental stimulation during developmentally sensitive periods (e.g., attention to faces during the early development of face processing systems), the abnormal developmental course of such infants

Table 1. *Candidate autism phenotype measures for QTL studies*

Trait	Brain Regions	Possible Measures	Examples of Published Family Studies	Examples of Published Linkage Studies
Face processing	Superior temporal sulcus Fusiform gyrus Amygdala Cerebellum	Standardized and experimental face discrimination/ recognition tests Latency and amplitude of N170 to faces and face movements	None	None
Sensitivity to social reward/ social affiliation	Amygdala, Ventromedial prefrontal cortex	Assessments of social preferences and friendships, personality ratings (e.g., aloofness)	Piven, Wzorek, Landa, Lainhart, Bolton, Chase, & Folstein (1994) Piven, Palmer, Landa, Santangelo, Jacobi, & Childress (1997)	None
Motor imitation	Superior temporal sulcus Broca's area Inferior parietal cortex	Neuropsychological and experimental tests of motor imitation	None	None
Declarative memory/feature binding	Medial temporal lobe/hippocampus Prefrontal cortex	Neuropsychological tests of declarative memory, deferred imitation, source and context memory, and feature binding (central coherence)	Happe, Briskman, & Frith (2001)	None
Executive function	Prefrontal cortex	Neuropsychological tests of planning and flexibility (ID–ED shift; Tower of London)	Hughes, Leboyer, & Bouvard (1997) Hughes, Plumet, & Leboyer (1999) Piven & Palmer (1997)	None
Language ability	Left temporoparietal cortex Broca's area Superior temporal gyrus	Age of language onset Standardized vocabulary and grammar tests Nonword repetition test	Folstein, Santangelo, Gilman, Piven, Landa, Lainhart, Hein, & Wzorek (1999); LeCouteur, Bailey, Goode, Pickles, Robertson, Gottesman, & Rutter (1996) Piven et al. (1997)	Bradford et al. (2001) Alarcon et al. (2002)

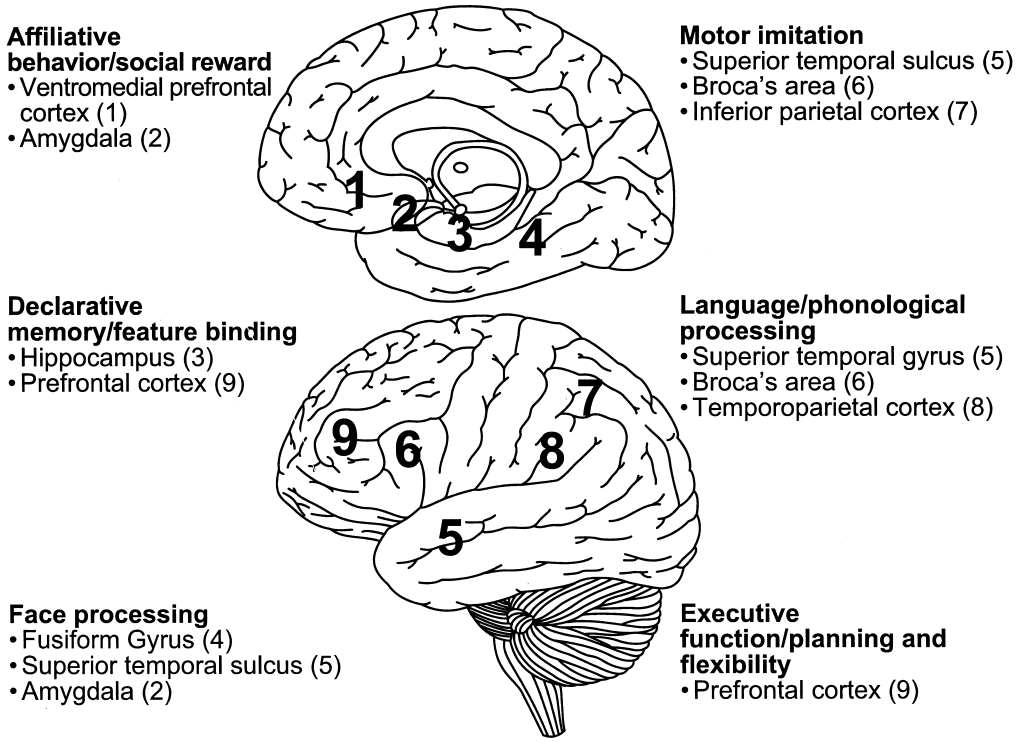

Figure 2. Candidate traits underlying the autism broader phenotype.

might be substantially improved by very early intervention. Such an outcome would be one of the many potential positive benefits that are likely to come from integrating knowledge across the fields of genetics, brain, and developmental/clinical science.

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