Autism Spectrum Disorders

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Autism as a Developmental Neurobiological Disorder: New Insights from Functional Neuroimaging

Points of Interest

- A paradigm shift in autism research, involving conceptualizing the syndrome as a developmental *neurobiological disorder* rather than a behavioral disorder, is critical to reconcile a gulf between behaviorally oriented researchers, clinicians, geneticists, and developmental neurobiologists and to address the most pressing questions about the etiology, brain bases, and effective treatments for autism spectrum disorders (ASD).
- A developmental neurobiological approach emphasizes a search for the underlying brain mechanisms when examining the manifestations of a disorder, which includes *both* the pattern of deficits as well as intact, or even enhanced, abilities and "associated signs and symptoms."
- An emerging body of genetic, functional and structural neuroimaging, and behavioral work suggests that defects in early neuronal organizational events during brain development disrupt the *connectivity of neural systems*.
- There appears to be a trade-off such that there is enhanced local neural connectivity, leading to preserved and potentially enhanced elementary information processing abilities, and disrupted connectivity among more distributed and integrative regions of the brain at the systems level, which leads to a deficit in complex information processing across multiple domains of functioning.
- Our investigations into the psychological mechanisms of visual processing in autism reveal relative preservation (and perhaps even enhancement, on some accounts) in more elemental, simple, or featural processing, whereas information processing that requires the integration of the simple elements is disproportionately affected. The imaging data yield a similar profile: relative preservation of earlier parts of the visual system and more pronounced atypical activation in higher-order regions. These alterations have a profound impact on how the brain in autism processes information and, in turn, how individuals with autism "see" the world differently.

With the first evidence of neurologic dysfunction in autism spectrum disorders (ASDs) in the 1950s and 1960s, there have been "neurobehavioral" theories were proposed to explain autism. These early theories typically focused on a behavioral feature of the syndrome and then inferred its relation to a localized region of the brain. These behavioral symptoms, or neurobehavioral deficits, were posited to be causally related to all other manifestations for the entire syndrome. These kind of localized region and single primary deficit theories for the cause of autism dominated the field for nearly 70 years, despite the recent structural and functional imaging evidence implicating widespread involvement of the cerebral cortex and associated white matter, and disruptions to functional neural systems. Importantly, this historical approach was not informed by an understanding of developmental neurobiologic events, particularly neuronal organizational events, in the developing brain, nor of knowledge about how disease processes affect the developing brain. As a result, there exists a conceptual and pragmatic gulf in autism research between 1) behaviorally oriented researchers and clinicians, who attempt to identify a causative feature of the syndrome that is anchored to impaired behavior, and 2) geneticists and developmental neurobiologists, who study genetic risk factors linked to disruption in neuronal organizational events.

In this chapter, we argue that a paradigm shift is critical to the study of autism in order to reconcile this gulf and address the most pressing questions about how genetic and developmental neurobiological findings can be integrated with findings about the characterization of the behavioral syndrome, which has become increasingly well defined in the last few decades. We propose that this paradigm shift involves conceptualizing autism as a *developmental neurobiological disorder* rather than a behavioral disorder when considering its

cause(s). The benefit of this approach is that it is informed by an understanding of basic principles of neurological disorders, including the notions that such disorders do not result in single primary deficits, that they typically have a genetic basis, and that, when they are nontraumatic or arise de novo, as in the case of ASDs, they are multiorgan system disorders. This approach also emphasizes a search for the underlying brain mechanisms when examining the manifestations, which includes *both* the pattern of deficits as well as intact, or even enhanced, abilities and "associated signs and symptoms." An emerging body of genetic, functional and structural neuroimaging, and behavioral work suggests that a potential underlying brain mechanism in autism is a disruption in the *connectivity of neural systems*. More specifically, due to defects in early neuronal organizational events, there may be a systematic trade-off between enhanced local neural connectivity within posterior and perhaps frontal regions of the brain, leading to preserved and potentially enhanced elementary information processing abilities, and disrupted neural connectivity among more distributed regions of the brain at the systems level, which may lead to a deficit in complex information processing across multiple domains of functioning. We review the evidence suggesting that a disruption in neural connectivity is fundamental in autism. Also, we highlight our own findings, particularly in the domain of visual processing, to illustrate the strength of our interdisciplinary approach that seeks to integrate and correlate genetic, neurobiological, and behavioral findings to understand the etiology, brain bases, and effective treatments for the complex disorder of ASD.

The chapter is organized as follows. First, we provide a brief review of the current "neurobehavioral" theories of autism. Second, we challenge these theories by reviewing current evidence, particularly from longitudinal studies of infants at high risk for developing autism, which challenges the notion of a single causative behavioral or cognitive feature of the syndrome or even a cluster of core causative behavioral or cognitive features. Third, we propose that research on ASDs would benefit enormously from taking the perspective that autism is a developmental neurobiological disorder, rather than a behavioral or single systems disorder. In this section, we describe the principles of neurologic disorders, the neuropsychological profile of autism, potential neural mechanisms of ASDs, including disruptions to neuronal events that fundamentally organize cortical systems during brain development, and the genetic factors that predispose individuals who go on to develop autism and are linked to disruptions in these early neuronal events. The key concept of this section is to demonstrate how this neurological approach to the study of autism leads directly to the search for underlying *brain mechanisms*, as opposed to behavioral phenotypes, that result in both the pattern of deficits and the intact abilities that are observed in ASD as well as the associated signs and symptoms of "comorbid disorders." Third, we review the evidence that a disruption in the connectivity of neural systems resulting from a disturbance early in neuronal organization is a likely candidate for such an underlying brain mechanism. Finally, we describe our program of research in the domain of visual processing that illustrates the strength of this interdisciplinary approach to uncover novel relations between the behavioral and brain bases of autism and that supports our claim that disruptions to neural connectivity are a fundamental contributing factor to the etiology of autism.

"Neurobehavioral" Theories of Autism and Challenges to Such Theories

The predominant single deficit models at present are the social primacy theories (e.g., Schultz, 2005; Klin et al., 2002; Dawson, 2008), and their alternative, the dimensional approaches (Happe & Ronald, 2008). The social primacy theories postulate that a social impairment comes first in time and is of sufficient severity to be viewed as causative of subsequent deficits, which are thus viewed as secondary to the social impairment. According to this model, autism is primarily, if not solely, a social-communication disorder both in terms of early etiological events and in terms of later presentation.

The dimensional hypotheses were proposed after investigators failed to find satisfactory evidence of a single or even a triad of primary deficits to account for the clinical syndrome, and hypothesized a cluster of independent core symptoms/signs that co-occur in autism but that are independently inherited (e.g., central coherence, theory of mind, executive function, repetitive behavior; Happe et al., 2006). These investigators tested their hypotheses by assessing typical populations for evidence of autism traits to ascertain their occurrence independently or in association with each other (Happe & Ronald, 2008; but see also Constantino et al., 2004).

Notice that both of these classes of "neurobehavioral" theories primarily focus on a functional analysis of *problematic behavior*. In other words, the central goal of these theories is to examine behavior to understand the cause of the disorder. A significant drawback of this approach is that focusing on describing an underlying mechanism is based on the behavioral impairments that present most severely, which may actually overestimate their significance in the etiology of the disorder. Furthermore, this approach does not emphasize an understanding of the abilities that are selectively preserved and even enhanced in the disorder. Our early work hinted that there are significant challenges to this approach and that the search for underlying brain mechanism(s) in autism must include an investigation of the profile of impaired *and* intact abilities.

Neuropsychological Studies Challenging Single Deficit and Dimensional Theories of Autism

Our initial approach to the investigation of autism was to pursue a comprehensive definition of the profile of functioning across all major neuropsychological domains, not just those that present with impairments in ASDs (Minshew et al., 1992; Minshew et al., 1997). We studied 33 individually matched pairs

of adolescents and adults with and without high-functioning autism (HFA), and assessed a broad range of abilities within each domain from the most basic to higher-order skills. Our original hypothesis was that the brain dysfunction causing autism diffusely and symmetrically involved altered development of connections with association cortex. We therefore proposed that higher-order abilities across multiple domains would be selectively affected. For this reason, elementary and higher-order abilities in all domains were assessed. At the time, there were some proposals of primary deficits in basic skills like elementary sensory perception, various aspects of attention, and basic associative memory abilities (see Minshew et al., 1997, for review of early theories). Assessments of nonverbal language and social abilities were not included in this study, since tests of these abilities in verbal individuals were not widely available at that time.

We found deficits across a number of domains, which enabled us to describe a broader pattern of deficits than had been previously reported in autism. The results revealed deficits in: skilled motor movements, higher cortical sensory perception, memory for material that required use of an organizing strategy or identification of an organizing strategy, higher-order language meaning, and concept formation. Notice that we identified deficits in several affected domains that were not previously considered to be integral parts of the autism syndrome, including aspects of the sensory-perceptual, motor, and memory domains. Hence, the evidence suggested that autism affected the brain far more generally than the single deficit and dimensional theories indicated. We also reported evidence of intact and sometimes enhanced abilities across multiple domains, including attention, elementary motor abilities, elementary sensory abilities, basic associative memory abilities, formal language skills (vocabulary, spelling, fluency, decoding), and the rule-learning aspects of abstraction. Again, unlike any previously reported findings, we observed enhanced skills and impaired abilities within the same domains (e.g., language). We have since completed an additional study with a younger sample of 56 children with autism and 56 controls that replicated this pattern of results with appropriate developmental modifications in the abstract reasoning domain (Williams, Goldstein, & Minshew, 2006).

Finally, we also evaluated single deficit theories about the role of cerebellar dysfunction in autism. We performed a study of postural control in 79 individuals with autism and 61 typical controls between 5 and 52 years. We observed delayed maturation of postural control and failure to achieve adult levels (Minshew, Sung, Jones, & Furman, 2004). The impairments were related to inadequate multimodal sensory integration across vestibular, visual, and position senses by the brain. There was no evidence of a cerebellar or motor contribution to postural instability in autism. These findings reinforced the notion that autism impacts neural connectivity and information integration very broadly and provided further evidence for the need to reconceptualize autism to accommodate these findings.

We were able to draw several conclusions from this constellation of findings. First, in all domains that we tested, the deficits were not in the acquisition of information as reflected in intact performance on multiple measures of attention, elementary sensory perception, and associative memory. In fact, we found that more elementary skills in each of these domains were intact or enhanced. Instead, the deficits selectively involved the most demanding aspects of information processing within each domain. Because the subjects were matched on gender, age, and IQ scores, this pattern of results indicated that the individuals with autism were unable to perform the more challenging tasks that might have been predicted based on their age and IQ scores and on their enhanced performance on the simpler tasks. We argued that this pattern of impairments and preserved abilities could be summed up as follows. First, the abilities that placed the highest demands on information processing or integration within the affected domains were most likely to be impaired, and the domains with the most prominent symptoms (concept formation, thematic and idiomatic language) were those that had the highest information processing demands. Hence, we proposed that the common denominator of the impaired abilities was the higher-order or "complex" information processing demands. Second, the abilities that were most likely to be preserved required elementary information processing demands (see Minshew, Webb, Williams, & Dawson, 2006, for detailed explanation). In sum, our early work challenged the "neurobehavioral" theories of autism primarily on the basis that they could not account for the comprehensive pattern of both deficits and intact aspects of the disorder both within and across multiple domains.

Beyond the Neuropsychological Profile of Autism

Our characterization of autism, based on all the neuropsychological testing, was that its manifestations reflected a disorder of information processing that disproportionately impacted complex information processing while preserving, or even enhancing, elementary information processing skills. This led to a novel hypothesis that we should observe an inverse relation between the impairments and the intact abilities at a neurobiological level as well (Kuschner, Bodner, & Minshew, 2009; Damarla et al., 2011).

We then began to investigate difficulties in information processing as a general construct. We pursued two lines of research. Because concept formation appeared common to impairments in conceptual understanding, cognitive memory, story theme creation and detection, and face recognition (in the sense of the requirement to integrate information for configural processing), we explored concept formation extensively. This line of research led to forays into the development and maturation of object categorization, the development of face identity and emotion recognition, and later the study of the emergence of these abilities in infants at high risk for autism (e.g., Best et al., 2010; Gastgeb et al., 2009; Gastgeb et al., 2006; Gastgeb et al., 2011; Humphreys et al., 2007; Iverson & Goldin-Meadow, 2005; Iverson & Wozniak, 2007; Newell et al., in press; Rump et al., 2009; Scherf, Behrmann, Minshew, & Luna,

2008). The second line of research focused on the area of visual information processing and used microgenetic techniques and fMRI studies to carefully investigate information processing in children, adolescents, and adults with autism (e.g., Behrmann et al., 2006; Hasson et al., 2009; Humphreys et al., 2008; Scherf, Luna, Kimchi, Minshew, & Behrmann, 2008; Scherf, Luna, Minshew, & Behrmann, 2010). Throughout this research program, we have considered how the profile of results implicates neurobiological mechanisms of brain development that could lead to atypical cortical specialization and a proclivity to use local rather than distributed representations for information processing. This approach was novel in the way we extended the definition of the syndrome to the neurologic realm and framed the issue in terms of information processing and integration, which was readily translatable to mechanisms within the brain and neural systems.

However, our findings were somewhat limited in the sense that they were conducted in children, adolescents, and adults, in whom a significant amount of brain and behavioral development had occurred. Given that ASDs are a developmental disorder first manifest in the first two years of life, it was critical to obtain earlier developmental data to truly and fully evaluate the explanatory power of the early "neurobehavioral" theories of autism.

High Risk Infant Studies Challenge Single Deficit and Dimensional Theories of Autism

Very recently, longitudinal studies of infants at high risk for developing autism (because they have an older sibling who has already been diagnosed with autism) have provided this critical early developmental data. These studies have been able to document the earliest identifiable signs of autism as emerging between 9 and 12 months of age (Rogers, 2009). Interestingly, the earliest identifiable manifestations of autism are not in the form of a primary social impairment, as the social motivation theories had long predicted, but instead in the form of unusual responses to sensory stimuli, unusual but subtle odd motor movements, and unusual visual regard for objects (Rogers, 2009). These findings were also inconsistent with the predictions of the dimensional theories. For example, Rogers (2009) explained:

> not only the core symptoms like joint attention deficits, repetitive behaviors, and language delays appear at 12 months and grow more severe over time, but even what were previously considered secondary symptoms—irritability, sensory responsivity, activity level, and poor gross motor development, are on board, and in some cases appear well before the social problems! These findings do not support the view that autism is [etiopathophysiologically] primarily a social-communicative disorder and instead suggest that autism disrupts multiple aspects of development rather simultaneously. (p. 133)

These longitudinal studies indicate that social and language impairments, long considered the *causative* features of autism, emerge later between 12 and 24 months. Furthermore, in some children, the diagnosis of autism could not be made until 2 to 3 years of age, when the classic symptoms and signs were obviously observable, and "it was particularly notable that disturbances in temperament, self-regulation, and hyperactivity emerged along side of these core symptoms," (Rogers, 2009).

These findings provide direct and clear evidence that there is no single primary deficit, brain region, or neural system causing autism, but also that a causative set of "core" symptoms is equally unlikely. Rather, Roger finds that autism broadly affects many abilities at the same time and systematically from its earliest presentation and continuing throughout life. This is exactly the view that we proposed previously based on our work with children, adolescents, and adults with autism (Minshew et al., 1992; Minshew et al., 1997; Williams, Goldstein, & Minshew, 2007). Additionally, the concept of associated and comorbid symptoms as representing the co-occurrence of other conditions is also clearly not supported by these data. This integrated perspective was particularly evident in the early observation of presentation of mental retardation and various regulatory disturbances in these infants and toddlers later diagnosed with autism. Rather, the evidence suggests that these conditions are part and parcel of the same disorder, resulting from atypical developmental brain processes (i.e., neuronal organizational events) that cause all the signs and symptoms of ASDs. Rogers concluded, "autism is not a disorder that profoundly affects social development from the earliest months of life. Rather, it is a disorder involving symptoms across multiple domains with a gradual onset" (p. 135).

Rogers made two more comments directly relevant to the present discussion. She noted that the high rate of autism and related manifestations in the infant siblings was striking, which supporting the importance of genetic contributions to its etiopathophysiology. To this she added that the absence of discernable behavioral manifestations at or before 6 months was likely a reflection of the limitation of behavioral measures in infants and the need for biologic measures in these early months.

Autism as a Neurological Disorder Rather Than a Behavioral Disorder

Given that there is significant evidence to discredit the notion that a single behavioral deficit, or even a core set of deficits, cause autism, we argue that a paradigm shift is critical to the study of autism. We propose that this paradigm shift involves conceptualizing autism as a *neurological and developmental neurobiological disorder* rather than as a behavioral disorder. There are several benefits of this approach, including that it is guided by an understanding of basic principles of neurological disorders, brain development, and how disease processes affect brain development. In this section, we briefly review principles of neurological disorders, the neuropsychological profile of autism, potential neural mechanisms leading to

ASDs, and the genetic contributions that may affect these neural mechanisms.

Principles of Neurological Disorders

Neurological disorders tend to conform to a common set of well known principles. First, such disorders produce a pattern or constellation of deficits and intact abilities that reflects the underlying disease mechanism. In other words, neurological disorders do not result in single primary deficits. The search for a single primary causal deficit of a neurologic disorder at the behavioral or cognitive level is not compatible with mechanisms of neurologic disease or dysfunction. Second, neurologic disorders that develop de novo (i.e., absent trauma or other injury) typically have a genetic basis. Hence, idiopathic autism is likely to have its origins in complex genetics (superimposed on the background of individual familial inheritance), as do innumerable other childhood neurological disorders that appear to have a sudden onset (e.g. see neuronal ceroid lipofucsinosis, which has three forms expressed at very different developmental time points from the first month to adolescence). Thus the work investigating genetic vulnerabilities for autism is critical for understanding the etiology of the disorder. Third, most nontraumatic neurologic disorders are *multiorgan system disorders* because they result from genetic errors that are present in all tissues in the body though not necessarily functionally expressed (Campbell et al., 2009).

To this set of core principles, we also add the concept that symptoms of a pediatric neurological disorder are expressed at a developmentally appropriate time window (i.e., when the affected skills are developing). Our characterization of the syndrome of autism is consistent with an emerging body of work that suggests that autism is largely a disorder of what neurologists call "higher cortical functions." Based on this characterization, it is to be expected that disruption in these higher-order functions becomes much more apparent in the second year of life when complex information processing abilities and their underlying neural systems are emerging.

We argue that research investigating the etiology of autism must focus on identifying aspects of the disorder that are consistent with tenets of neurological disorders. Furthermore, based on the existing work, we suggest that the focus of such an approach should be on discerning known neurological and neurobiological mechanisms for disruption to the development of higher cortical brain functions.

Developmental Neurobiologic Mechanisms and the Clinical Syndrome of Autism

ASDs are becoming increasingly recognized as developmental neurobiological disorders (Geschwind & Levitt, 2007; Minshew, Williams, & McFadden, 2008; Volpe, 2008). The notion that a disturbance in a developmental neurobiological mechanism could cause autism is consistent with early reports of truncated dendritic tree development in hippocampal neurons (Bauman & Kemper, 1994), increased brain weight in children and decreased brain weight in adults (Bauman & Kemper, 1998), and premature acceleration in head growth at 9 months followed by a plateau in growth (Dawson et al., 2007). In particular, it is likely that a developmental neurobiological mechanism that guides or regulating *neuronal organizational* event is strongly implicated in the etiology of autism.

Neuronal organizational events are described in clinical neurology texts as "the sequence of organizational events that result in the intricate circuitry characteristic of the human brain" (Volpe 2008, p. 51). In fact, autism is now described as a clinical example of a neuronal organizational disorder (Volpe, 2008). Neuronal organizational events occur between 5 months gestation and many years if not decades after birth. The neuronal laminar pattern is established by 3 years of age, and the bulk of the cortical axonal density is present by 12 years of age. "The major developmental features of neuronal organization events include the following: 1) the establishment and differentiation of subplate neurons; 2) attainment of proper alignment, orientation and layering of cortical neurons, 3) the elaboration of dendritic and axonal ramifications, 4) establishment of synaptic contacts, 5) cell death and selective elimination of processes and 6) proliferation and differentiation of glia" (Volpe, 2008, p. 82). When reviewing histologic displays of cortical neurons and images of the whole brain and cortex undergoing maturational events from 22 weeks gestation through several years postnatal age, it becomes apparent that organizational events have a widespread impact throughout the cerebral cortex, and are more symmetric than not. The cerebral cortex goes from a nearly smooth surface to a highly folded surface in the last trimester; organizational changes in the cortex and brain continue long after birth. These events are responsible for the amazing capacity of cortical neurons to send and receive innumerable connections within and between hemispheres and to ultimately form the systems level organization responsible for the many specialized functions of the human forebrain.

The aspects of brain development that have been most clearly implicated in autism are neuronal organizational events, though some cases have also implicated neuronal migration events (Strauss et al., 2006; Volpe, 2008). In addition, ASD has been identified in 20–30% of young children with cerebral palsy who were extremely premature (born at or before 28 weeks gestational age) at birth (Moster et al., 2008), a time in brain development when neurons destined for the cerebral cortex are in the periventricular region. The periventricular region is also the premature infant's the watershed zone, or vulnerable region during compromised vascular perfusion of the brain in extreme premature infants. This pathophysiology raises the possibility that a stroke induced disturbance in neuronal number and/or in early neuronal migrational events during which neurons travel from the periventricular region to cortex might be the basis of the autism syndrome in association with cerebral palsy (Kuban et al., 2009; Minshew, 2010 in press, 2011; Volpe, 2008).

Though research studies have demonstrated widespread disturbances in cortical functioning in ASD, the disturbances are also somewhat selective. The cellular basis for this selectivity is

not yet known other than that the disturbance involves cerebral cortical neurons that are involved in forming *distributed systems*. The developmental neurobiological events that produce the development of this circuitry are highly genetically regulated. It is reasonable to expect that the process of identifying genetic causes of ASD (and carrier status) will unfold the same way as did the causes in other child neurological disorders. That is, ASDs will be found to result from numerous related errors in the genetic code for a selected aspect of neuronal organization, just as many other childhood neurological disorders that develop de novo have been found to be the result of groups of abnormal genes. An error in the genetic code for a fundamental aspect of neuronal organization could potentially produce a broad profile of similar deficits (e.g. autism versus William's syndrome; Minshew, 2010; see also Volpe, 2008, pp. 82–102).

Genetic Foundations of ASDs

Developmental neurobiological events are extraordinarily complex, require precise guidance, and are known to be under strict genetic control (see Chapter 30 by J. Rubenstein, in this volume). Currently, approximately 20 or so mostly rare genes (and an occasional common gene or gene sequence) have been discovered that contribute to the cause up to 15–20% of cases of autism and ASD (Abrahams & Geschwind, 2008; Bolton, 2009; see also Commentary by Geschwind in this volume). Though "heterogeneous," these genes have in common a role in the development of connectivity among neurons and share common molecular signaling pathways (Geschwind & Levitt, 2007; Minshew, 2010a; Minshew, Williams, & McFadden, 2008).

The identification of these genes followed two decades of neuroimaging research establishing premature acceleration in brain growth as measured by total brain volume, including cerebral gray and white matter, followed by growth deceleration (reviewed in Levy et al., 2009; Mosconi, Zwaigenbaum, & Piven, 2006; and Chapter 35 in this volume). These are classic signs of disturbances in developmental neurobiological events. Furthermore, this research has also indicated disruptions in connectivity of cortical systems as a major etiopathophysiologic mechanism in autism and ASD (summarized in Minshew & Williams, 2007; and Chapter 54 in this volume). The convergence of genetic and neuroanatomical evidence for neuronal connectivity disturbances provides strong support for the notion of a developmental neurobiologically based model of autism and the ASDs. Imaging genetics, a comparison of genotype variability with imaging and behavioral phenotype variability, holds promise for additional insight into genetic contributions to the heterogeneity of the behavioral expression of the syndrome (see, for example, Raznahan et al., 2009; Wassink et al., 2007). In the discussion above, autism and ASD were referred to separately to indicate that the gene mutations were often found to be associated with both autism and ASD, often in the same families, supporting common underlying neurobiological and genetic mechanisms rather than separate etiologies for autism, Asperger's disorder, and Pervasive Developmental Disorders Not-Otherwise-Specified.

The identification of genes in autism has led to a number of major advances. The first is the development of a molecular pathophysiology for syndromic autism (e.g., tuberous sclerosis and TSC1 TSC2 genes, 22q deletion and SHANK3 gene, Rett syndrome and MECP2 gene, Fragile X syndrome and FMR1 gene, Timothy syndrome and CACNA1C gene), and some instances of nonsyndromic autism, (e.g., NRXN1, MET, and NLGN3; Abrahams & Geschwind, 2008). The development of animal models of these genes (primarily gene-neuroanatomical relationships with limited cognitive-behavioral correlates of autism) is enabling the development and study of neurobiological interventions (for example: Dolen et al., 2007; Ehninger & Silva, 2011; Silva & Ehninger, 2009), which confirm a connection between gene-to-brain development and autism-ASD phenotypes. This line of research has led directly to clinical trials with Rapamycin, an mTor inhibitor, for prevention of seizures, mental retardation, and ASD in infants and toddlers with genetically diagnosed tuberous sclerosis (Ess, 2009; Nie et al., 2010), providing clear proof of concept of the merits of uncovering molecular mechanisms for brain dysfunction in ASD. Animal models also provide opportunities for investigating potential molecular and cellular mechanisms of cortical dysfunction, such as the hypothesized role of an excitatory-inhibitory imbalance as a mechanism of cortical dysfunction and seizures in autism (Gogolla et al., 2009).

Another line of research supporting a developmental neurobiological model and connection between gene abnormality, cortical development, and manifestations of ASD has been the *MET* receptor research. This work was initiated as a result of reports of an increased association of the *MET* receptor CC allele with autism (Campbell, Sutcliffe, Ebert, et al., 2006; Campbell, Sutcliffe, Persico, & Levitt, 2008). Subsequently, researchers discovered increased *MET* mRNA expression levels in ASD brains (Campbell, D'Oronzio, Garbett et al., 2007), correspondence between *MET* mRNA levels in temporal lobe in ASD and language status (Campbell, Warren, Sutcliffe, et al., 2009), and correspondence between the presence of the *MET* gene and presence of gastrointestinal difficulties in ASD individuals (Campbell, Buie, Winter, et al., 2009) all provided additional support for a critical role of the MET receptor gene in autism. The *MET* receptor gene codes for cortical and cerebellar development, gastrointestinal repair, and immune competence (Campbell et al., 2006; Campbell et al., 2007), thus providing an example of a single genetic explanation for multiple organ involvement in ASD. Together, this body of imaging and genetic findings in ASD over the past decade has established a firm foundation for autism as a developmental neurobiological disorder and has identified a number of genetic abnormalities and mutations likely to be causative, which, though "heterogeneous," share signaling pathways at a molecular level involved in the development of neuronal connectivity (Levitt & Campbell, 2009).

The rapid growth in gene technology makes it highly likely that the list of ASD causative and associated genes will expand quickly and, with it, the delineation of a highly complex and heterogeneous molecular pathophysiology for autism. It is also likely that the growing number of gene variants and

mutations discovered in ASD will nonetheless be found to contri-bute to a select number of common neuronal signaling pathways involved in developmental neurobiological events that result in the connectivity disturbances and growth dysregulation that is now well documented in autism (Minshew, 2010a). It is also likely that increasing knowledge about the variation in implicated genes will account for the variability in brain growth trajectories that has been observed in autism and ASD (Lainhart et al., 2006), as well as the variability in symptom severity. Greater genetic and developmental neurobiological diversity can be expected in very low functioning individuals with ASD, since there is less specification or restriction of events that can result in the absence of functional cortical connectivity compared to genes that are very selective in their impact on cortical connectivity.

With all of this in mind, the next question is how to connect the genetic and developmental neurobiological findings with the behavioral syndrome, which has been defined in growing detail over the past seven decades. Thus far, the answer has been found in altered development of cortical systems connectivity in autism.

Disruptions in Cortical Connectivity as the Brain Basis for Autism

Given 1) our previous findings of a simple-complex dissociation in the neuropsychological profile of autism with deficits in higher-order abilities across multiple domains and 2) the work implicating a disruption in neural organization events related to particular genes; we launched a program of research to investigate the role of disruptions in *cortical connectivity* as the brain basis of autism.

Language Domain

One of the simple-complex dissociations that we and many others have observed in autism in the language domain is that many individuals are superb spellers but have trouble understanding sentence meaning. Understanding this dissociation became the basis for our first functional neuroimaging study that resulted in a theory proposing cortical functional underconnectivity in autism (Just, Cherkassky, Keller, & Minshew, 2004). We used fMRI to measure brain activation in adults with high-functioning autism and typically developing, verbal, IQ-matched controls as they read sentences. The autism group exhibited increased activation in Wernicke's area, but reduced activation in Broca's area compared to controls. These findings map onto the behavioral profile of increased word knowledge and reduced sentence knowledge in the participants with autism. Furthermore, the functional connectivity (i.e., the degree of synchronization or correlation of the time series of the activation) between these cortical areas was consistently lower for the autism than the control participants. These findings suggested that the neural basis of disordered language in autism entails a lower degree of information integration and synchronization across the large-scale cortical network for language processing. This was the first of many subsequent studies showing a reduced collaboration among a network of cortical regions that support higher order function. It was a critical first step in support of our theory that connectivity within and between cortical systems is fundamentally underdeveloped and may be a central pathophysiologic mechanism for autism (see Chapter 54 in this volume).

Alterations in Connectivity More Broadly in the Brain

Subsequent studies also demonstrated reduced connectivity between posterior cortical regions and frontal cortex, and more bilateral activation within posterior visual and visuospatial cortex than occurs in typically developing individuals (Kana, Keller, Cherkassky, et al., 2009; Koshino, Kana, Keller, et al., 2008; Sahyoun, Belliveau, Soulieres, et al., 2010). We have proposed that these findings reflect underdevelopment of systems-level connectivity between cortical regions and frontal cortex, as well as enhanced local connectivity within visual cortex (see next sections on visual processing in autism). Other investigators have documented underdevelopment of cortical connectivity with amygdala and related circuits to account for the fundamental disturbances in affective contact in autism, and alterations in frontal-amygdala and striatal connections to account for difficulty in comprehending and regulating emotions (Gaigg & Bowler, 2007, 2008; Kleinhans et al., 2008). Analogous disturbances have been demonstrated in motor systems connectivity (Mostofsky et al., 2009).

Underconnectivity of cortical systems is now a widely accepted characterization of the structural and functional brain abnormality in autism. The initial index of functional underconnectivity was reduced synchronization between fMRI-measured activation in coactivating cortical areas during a sentence comprehension task (Just et al., 2004), which was subsequently demonstrated across a wide range of tasks to broadly involve cerebral association cortex (Just et al., 2007; Schipul et al., 2011). Over the course of many studies, *frontal-posterior* underconnectivity emerged as a common finding (Kana et al., 2009). The second characteristic of the altered task-related cortical connectivity in autism was enhanced activation of occipitoparietal areas. This activation pattern was hypothesized to result from *increased local connectivity* in posterior regions and to account for the unusual strengths also typical of autism. The dissociation between impaired higher order skills and intact basic skills was commonly characterized in the past in terms of a distinction between verbal and visuospatial abilities, rather than in terms of reduced frontal and enhanced posterior neural connectivity.

A recent fMRI study of the neural networks underlying visuospatial and linguistic reasoning has provided direct evidence that verbal individuals with average IQ scores and HFA have increased activation and connectivity of occipitoparietal and ventral temporal circuits, greater reliance on visuospatial

skills for solving both visual and verbal problems, and reduced activation and connectivity of frontotemporal language areas (Sahyoun, Beliveasu, Soulieres, et al., 2010). The study concluded that the HFA group's engagement of posterior regions along with its weak connections to frontal language areas resulted in reliance on visual mediation even for higher order cognitive tasks. This study recapitulates the findings of the connectivity studies and adds some of the clearest evidence yet to support the neural basis of the visuospatial processing strengths in autism.

One outstanding and perhaps puzzling issue concerns the underconnectivity (defined here as reduced correlation in activation profile between two areas of cortex) between cortical regions and the concurrent evidence for increased white matter connectivity between disparate cortical regions in ASD. For example, in one of our recent studies with high functioning autistic adults, we observed an increase in white matter connectivity in long intrahemispheric fibers such as the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus, but not in the homotopic callosal fibers (Thomas et al., 2010). One might have predicted that an overproliferation or overabundance of white matters fibers would be associated with an increase in cross-areal correlation and yet the studies, such as Kana et al. (2009), suggest otherwise. A possible resolution to this apparent discrepancy between the reduced correlations and the increased white matter tracts is that the signal propagated across the increased tracts may not have sufficient fidelity with the consequence that the correlation across regions will be substantially impeded.

Understanding the Neurobiological Substrates of Autism Through Studies of Visual Information Processing

Many of our studies conducted over the last few years have focused on the cortical visual system of individuals with ASD and have provided converging evidence for the claim that sensory-perceptual function evinces the same simple-complex dissociation, as described in other more abstract domains such as language. Because the same dissociation between simpler versus more complex information processing is evident in the visual system in ASD, we think the same underlying neurobiological process is likely implicated. Thus, whereas more elementary visuoperceptual skills are preserved, or possibly even enhanced (Ashwin et al., 2009; Mottron et al., 2006; Mottron et al., 2009; Soulières et al., 2009) relative to typical controls, more complex information processing requiring the synthesis of disparate bits of information is disproportionately impacted. We begin this section by reporting data from visuoperceptual processing in adults and in children with autism and then turn to describe a series of recent imaging investigations conducted with the same populations. The associated imaging investigations, which we describe, also offer supportive evidence for a biological system in which local or short-range connectivity is better preserved but longer-range connectivity especially with multi-modal association cortex and in particular with frontal cortex, necessary for integration at the neural and information processing level, is compromised.

Visual Processing: Behavioral Studies

One of the most essential visuoperceptual skills for humans is face processing. Interestingly, impairments in face processing are a widely accepted aspect of the behavioral profile of autism. The impairment involves difficulty remembering faces (Boucher & Lewis, 1992), processing facial expressions (Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007), and knowing which components of faces convey especially important communicative information (Joseph & Tanaka, 2003). One of the key behavioral processes considered critical for intact face perception is the ability to perceptually organize, or integrate, disparate components of the input rapidly and efficiently. Moreover, the failure to do so impacts both facial identity and emotional expression recognition. Both face perception and perceptual organization have been shown to be compromised in autism, and the studies we describe below document the atypicalities in both domains and suggest an association between the difficulties in these processes in individuals with autism. We start off by examining the *local processing bias*, or enhancement, in individuals with autism and then discuss the difficulties in face perception.

In contrast with the documented difficulties in higher-order perceptual abilities, such as those engaged for face processing (Gastgeb et al., 2011; Klin et al., 2002; Joseph & Tanaka, 2003; Humphreys et al., 2008; Lahaie et al., 2006; Pellicano et al., 2007; Scherf, Behrmann, et al., 2008), individuals with autism have been shown to exhibit hyper- or enhanced sensitivity to the more simple local elements of the input (Mottron et al., 2009; Soulières et al., 2009). For example, compared to age-matched, typically developing individuals, those with autism exhibit superior abilities to detect local targets in visual search tasks (Plaisted et al., 1999), ignore the influence of increasing numbers of distracters during visual search (O'Riordan et al., 2001), and identify fine stimulus features in spatial tasks like the Wechsler block design and Embedded Figures Task (Shah & Frith, 1993; Jolliffe & Baron-Cohen, 1997), to name but a few such observations. At the same time, individuals with autism appear to be limited in their ability to derive organized wholes from perceptual parts, which has been linked to their limited use of gestalt grouping heuristics (Brosnan et al., 2004), the failure to process inter-element relationships (Behrmann et al., 2006), and/or the failure to consider the entire visual context (Happé, 1996). Several studies have argued that this focus on local features is specifically detrimental to face recognition processes (Hobson et al., 1988; Boucher & Lewis, 1992; Davies et al., 1994; Klin et al., 2002; Joseph & Tanaka, 2003; Lahaie et al., 2006), and we consider this further below.

Although there is general consensus that the perceptual abilities of individuals with ASD are atypical (for review see Behrmann et al., 2006; Dakin & Frith, 2005), there still remains some controversy both about the nature of the atypicality as

well as the source of this atypicality. Some researchers have suggested that children with autism exhibit limited abilities to integrate local elements into a coherent global shape (Plaisted et al., 1999; Rinehart et al., 2000; Wang et al., 2007), whereas others have reported typical processing of both the global and local information in hierarchical visual stimuli (Ozonoff et al., 1994; Mottron et al., 2003; Iarocci et al., 2006; Plaisted et al., 2006).

To explore both the difficulty in global organization and perhaps the undue focus on local elements, in a recent study (Scherf, Luna et al., 2008b), we conducted two related investigations in children, adolescents, and adults with high-functioning autism (HFA) and age- and IQ-matched typically developing (TD) controls, using a well-known task of global/local processing with compound letter stimuli as well as a more novel, fine-grained microgenetic priming paradigm with hierarchical shapes including both few and many local elements.

In the first investigation, we employed the well-known hierarchical compound stimuli (Navon, 1977), which included global letters composed of smaller local letters that were either consistent or inconsistent with the global letter in identity (see Figure 36-1A). This design allows for performance measures, such as the speed of identification and asymmetric interference during inconsistent trials (for example, a global 'H' made of small 's's), to be used to infer the advantage of one level over the other (Navon, 1977, 1983). Participants were required to respond by key press (is an H or S present) to indicate letter identity. Identification of the global or local letter was required in different blocks of trials. As expected and as predicted from well-established findings, the typically developing (TD) adults were faster to identify letters at the global level (for example, a global 'H' made of small 's's) than at the local letter (for example, the small 's's in the global 'H'), reflecting the so-called forest before the trees finding and indicating a bias to perceptually organize the disparate local elements to perceive the global letter. Importantly, this bias to perceptually organize the local elements increased linearly with age in the TD group. This pattern of results was not true for the HFA group, who was faster to identify letters at the local level, clearly revealing the bias to perceive the local (trees) rather than global (forest) arrangement of the letters. These findings are consistent with the idea that the emergence of the local processing bias in autism becomes prominent in adolescence and never transitions into a global bias in adulthood as in the TD individuals.

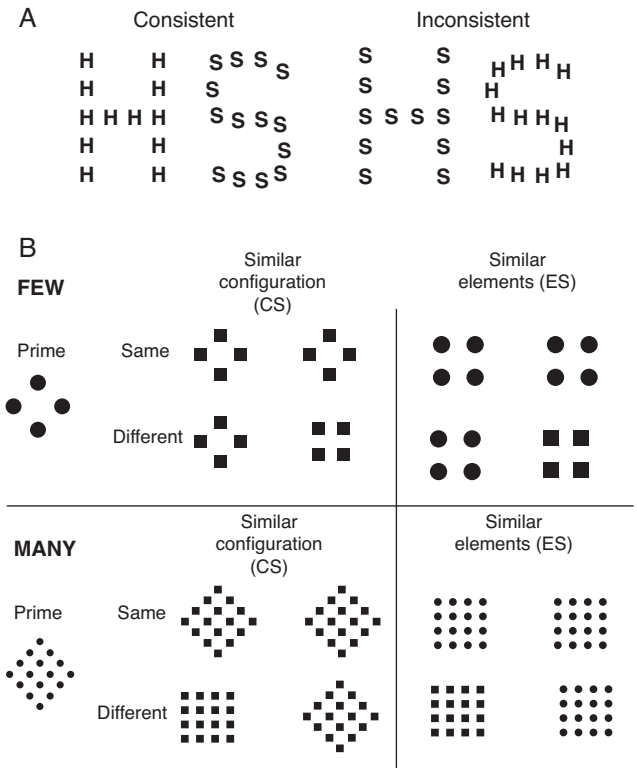

Figure 36–1. A) The compound letter stimuli used in the global/local task to evaluate developmental differences in sensitivity to global (big letter) and local (small letters) information. B) The hierarchical shape stimuli used in the microgenetic priming task (few- and many-element).

To confirm these findings, we conducted a second study in the same participants and, in this investigation, we assessed the temporal evolution of the organized visual percept, instead of simply measuring reaction time to identify a global or local letter as we had done in the first investigation reported above. To do so, we adopted a paradigm developed by Kimchi (1998, Expt 1) to test perceptual organization processes in typical adults. In this paradigm, participants view (but ignore) an ambiguous prime (for example, a diamond made of four circles in the "few" element condition or a diamond made of many circles in the "many" element condition) followed immediately by a pair of test figures (probes). Participants are required to judge whether the two probe images are the same or different and to indicate their response by key press. As evident from Figure 36-1B, both the prime and probe stimuli include patterns (i.e., global diamonds composed of smaller circles) with few large elements or with many small elements. Each test stimulus includes two probes from one of two conditions, defined by their similarity to the prime stimulus (see Figure 36-1B). In the *element-similarity* (ES) condition, probes are similar to the prime in their local elements (circles), but differ in their global configuration (global square instead of global diamond). In the *configuration-similarity* (CS) condition, probes are similar to the prime in their global configuration (diamond), but differ in their local elements (local squares instead of local circles).

The (ignored) prime is presented at several durations, providing multiple temporal windows over which the representation evolves prior to the onset of the probe, and behavioral responses are compared across the prime durations. The expectation is that, at short prime durations, only the most dominant characteristic of the percept of the priming stimulus is represented (e.g., for the few element stimuli, only the local information may be represented this early). When the test figures share these entry-level or early characteristics with the prime stimulus, responses will be facilitated. At longer prime durations, it is possible that both local and global characteristics are represented, in which case the prime would enhance

both of these dimensions in responses to the test figures. Because we know that grouping into a whole is easier when there are many local elements, we expect there to be an advantage for the configuration-similarity probes for the many versus few elements and this advantage may even manifest at early prime durations, reflecting the rapid organization into a gestalt in the typical visual process.

Unsurprisingly, we replicated the original Kimchi (1998) data, and showed that it takes longer (at longer prime durations) for the TD adults to evince an advantage for the "few" *configuration-similarity* (CS) condition both because the local elements are few and prominent in their own right, but also because they are somewhat spatially distant and have to be integrated to form a global whole and this is perceptually demanding. Of particular importance to us here, and again like the Kimchi data, these TD adults encode global shape information in the entry-level units (at very brief prime durations) of the representation for the "many" element displays, indicating the rapid and efficient integration of local information and access to global shape information. The question then is how individuals with ASD fare under these experimental conditions.

We found that HFA adults are faster to make similarity judgments about test figures that share local elements (ES trials) rather than global shape information (CS trials) with the prime, regardless of the prime duration or the number and size of the elements (Behrmann et al., 2006; also reported in Scherf, Luna et al., 2008). These results indicate that, in the HFA adults, both the entry-level units and the final percept of hierarchical visual stimuli are dominated by information about the local elements, regardless of whether the elements are few and large or small and many. This result is consistent with the data from the first investigation using compound stimuli in which the local bias dominated performance in the HFA individuals, even in the adults with HFA. The same investigation with CS and ES test trials conducted with HFA adolescents and children revealed a similar finding to that of the HFA adults: they are faster to say "same" to the *element-similarity* (ES) probes across nearly all exposure durations. Thus, not only do they **not** glean the advantage for the configuration at early prime durations, but, interestingly, they show a much greater advantage for the element similarity probes than do their matched controls, perhaps reflecting the hypersensitivity to the local elements (even though they are many and small).

In the few-element displays, children, adolescents, and adults in both groups were biased to encode the local elements, regardless of the prime duration, indicating that the ability to individuate elements presented in hierarchical displays with few, large items matures quite early in both TD and HFA populations. These results suggest that, beginning in childhood, local information dominates the formation of a percept in autism from the entry-level units to the longer-term visual representation, regardless of the stimulus characteristics of the local elements. Furthermore, the ability to group local elements perceptually in order to perceive a global shape does not appear to mature during the developmental transition from adolescence to adulthood in HFA as it does in TD individuals, as was apparent in the results from the many-element condition.

In sum, the findings from both the few- and many-element displays indicate that local information dominates the formation of a percept in children, adolescents, and adults with autism regardless of whether the local items are few and large or small and many. The local information is encoded in the entry-level units of the percept (results from short prime durations) and organizes the final percept (results from long prime durations). We only found evidence for superior processing of local information in the many-elements task, which is present by childhood. TD children, adolescents, and adults encode more global shape information from the many-element displays (as evidenced by their weaker ES advantage), while those with autism exhibit enhanced perception of the local elements. The atypical development of these perceptual organizational processes in ASD may contribute directly to disruptions in the processing of visually presented objects, which may, in turn, fundamentally influence the development of major aspects of the social and emotional deficits characteristic of autism (see New et al., 2010, for recent discussion of social deficit and complexity of this deficit). We go on now to explore the relationship between the obvious local bias and higher order pattern recognition in ASD.

These atypical perceptual organizational processes, we have argued, may contribute to the difficulties in more complex visual processing, such as face perception, in ASD. In particular, ASD individuals may be more focused on local elements of faces and less able to integrate the elements into a whole. This process of integration is thought to become even more critical when faces are similar and the featural differences themselves do not suffice for differentiation. The focus on local aspects of faces is well captured in this comment by Temple Grandin:

> I often get into embarrassing situations because I do not remember faces unless I have seen the people many times or they have a very distinct facial feature such as a big beard, thick glasses or a strange hairstyle. (*Thinking in Pictures and Other Reports from My Life with Autism* by Temple Grandin)

To evaluate whether the same HFA individuals who showed an undue local bias in the compound letter task and micro-genetic task described above also show a difficulty in face recognition, especially as faces become more similar to one another, the same adults with HFA who participated in the studies above, made same/different judgments to two faces presented alongside each other, for unlimited duration, in the center of a computer screen. On "different" trials, the faces could be either two faces from different genders or, in the more perceptually taxing case, two different faces of the same gender (see Figure 36-2a). It is in this latter condition that the reliance not only on featural information but also on the second-order relational information among the features becomes even more necessary. As shown in Figure 36-2b, not only were the ASD adults slow at making the similarity judgments, but they were disproportionately slower for judging the more

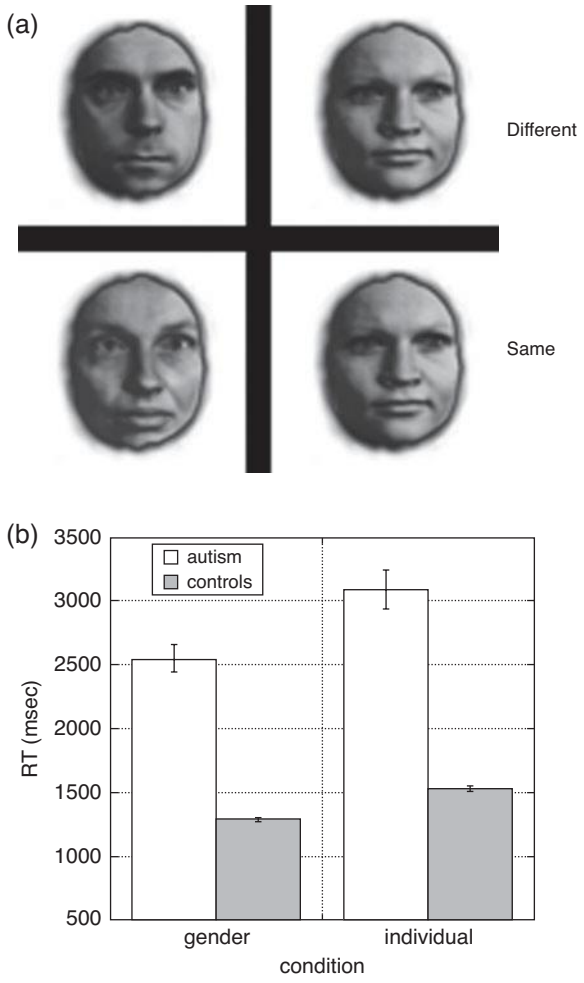

Figure 36–2. a. Examples of stimuli for face discrimination experiment, including one trial where faces differ on the basis of gender and one trial where faces differ on the basis of individual identity. b. Mean of median RT (and 1 SE) for correct different trials as a function of conditions of discrimination for autistic and control groups.

similar faces (albeit a "different" judgment). Taken together, these behavioral findings not only reveal the slow responses in face perception in the HFA adults, but also the disproportionate difficulty in the more demanding face task that requires perceptual binding of the elemental features.

We have shown atypical perceptual processing in tasks requiring holistic grouping or binding of elements and we have shown disproportionate slowing in face discrimination in the same individuals. To establish whether there is any association between performances on these two tasks, we took the median RT for each HFA individual on the "individually different/same gender" and correlated them with the local advantage from the compound hierarchical letter task. This analysis yielded a significant r^2 value of .61 ($p = 0.03$). Although correlation is not causation, the relationship between RT in face processing and the local bias is clear in the autistic adult individuals and is highly suggestive of some common atypicality.

In sum, the behavioral data we have reported here document not only the advantage for processing local elements in individuals with HFA across the age span but also the association between the local bias and the difficulty making fine-grained discrimination between faces. The view we have taken here is that the slowing in face processing in autism, a higher-order visual task that requires the integration of many local elements, might arise from a more fundamental visual (and possibly even sensory-independent) bias toward the local elements and perhaps simultaneous or resultant difficulty in integrating local components of a stimulus into a whole. We have also argued that this fundamental perceptual form of processing is likely not restricted to faces but may impact visual processing of other, nonface objects, too, when the demands for discrimination and recognition are high, as is true in the case of faces (Behrmann et al., 2006; Scherf, Behrmann, et al., 2008).

These findings are not easily accounted for by views that argue for a primary social, rather than perceptual, deficit in autism. The perceptual deficit that we and others have documented may exist independently of a social deficit. Alternatively, perceptual and social deficits may work in tandem: the lack of experience and the inadequate attention to faces may limit the acquisition of the normal configural perceptual skill and/or the perceptual deficit may constrain the ability to acquire typical face representations (see also Grelotti et al., 2005). Either way, there appears to be some fundamental dissociation between the ability to process local elements and the ability to integrate these elements efficiently for higher order pattern perception.

Visual Processing: Imaging Investigations

In our pursuit to understand the relation between the neurobiological and behavioral manifestations of autism, we have also undertaken several functional neuroimaging studies of visuoperceptual processing in adults and adolescents with autism.

Activation of Earlier Versus Later Visual Cortex.

One prediction that arises from the behavioral studies is that individuals with ASD should show reduced or minimal activation of those regions of visual cortex that support higher-order visual perception, while earlier parts of the visual system should remain intact. Our own experiments have focused on the former point, although there are good data to suggest that there is preservation (even if not totally normal activation) of the earlier parts of the visual system (Hadjikhani et al., 2004). We also note that some recent investigations have suggested enhancement of activation in earlier parts of the cortical system (Mottron et al., 2006), and a recent study reports an increase in grey matter in auditory and visual primary and associative perceptual areas. These last results demonstrating potential structural brain correlates of atypical auditory and visual perception in autism provides possible support for the enhanced perceptual functioning model (Mottron, Dawson, Soulières, Hubert, & Burack, 2006; Mottron, Dawson, & Soulières, 2009).

Consistent with the claim that higher-order regions of visual cortex (such as the fusiform gyrus or "fusiform face area"; FFA) are engaged in face processing, and that individuals with autism do not respond preferentially to faces, many studies (Corbett et al., 2009; Critchley et al., 2000; Schultz et al., 2000; Pierce et al., 2001; Hall et al., 2003; Hubl et al., 2003; Humphreys et al., 2008; Ogai et al., 2003; Piggot et al., 2004; Wang et al., 2004; Dalton et al., 2005; Grelotti et al., 2005; Deeley et al., 2007) have found reduced BOLD activation in the fusiform face area (FFA, Kanwisher et al., 1997). However, other studies have failed to replicate this finding (Hadjikhani et al., 2004; Hadjikhani et al., 2007; Pierce et al., 2004; Bird et al., 2006), and so there remains some controversy surrounding the brain-behavior correspondences in FFA and ASD.

To explore the integrity of higher-order visual cortex and to map out cortical activation for faces in a broader network that extends beyond the FFA to include the occipital face area (OFA) and superior temporal sulcus (STS), but also for other images such as places and objects, ASD and TD adult participants viewed naturalistic, real-time movies of unfamiliar faces, buildings, navigation through open fields, and objects in a blocked fMRI paradigm (Figure 36-3a; Humphreys et al., 2008). Rich, moving stimuli from multiple categories, such as these (see Figure 36-3a), have been shown to induce stronger activation in ventral cortex than do static, black and white images, and so we used them to increase our chances of uncovering robust cortical response profiles in the HFA group. We also note that this task has been used successfully to map category-selective activation in the ventral visual cortex in other populations (Hasson et al., 2004; Avidan et al., 2005; Scherf et al., 2007). There are no specific task demands in this investigation, and so performance differences between the autism and comparison groups cannot account for any different levels of functional activation.

Figure 36-3b shows the average activation maps for the autism and typical adults in this experiment projected into a single inflated brain with both lateral and ventral projections. Note that we group together the building and scene related activation, as both typically activate the parahippocampal place area (PPA) in the collateral sulcus (Scherf et al., 2007). The findings from the typical group largely replicate the standard findings with extensive activation for faces (red) and objects (blue). The building/scene-related activation (green) in PPA appears somewhat reduced, especially in the left hemisphere but this has been noticed in other studies as well (Avidan et al., 2005). The most marked feature is the clear

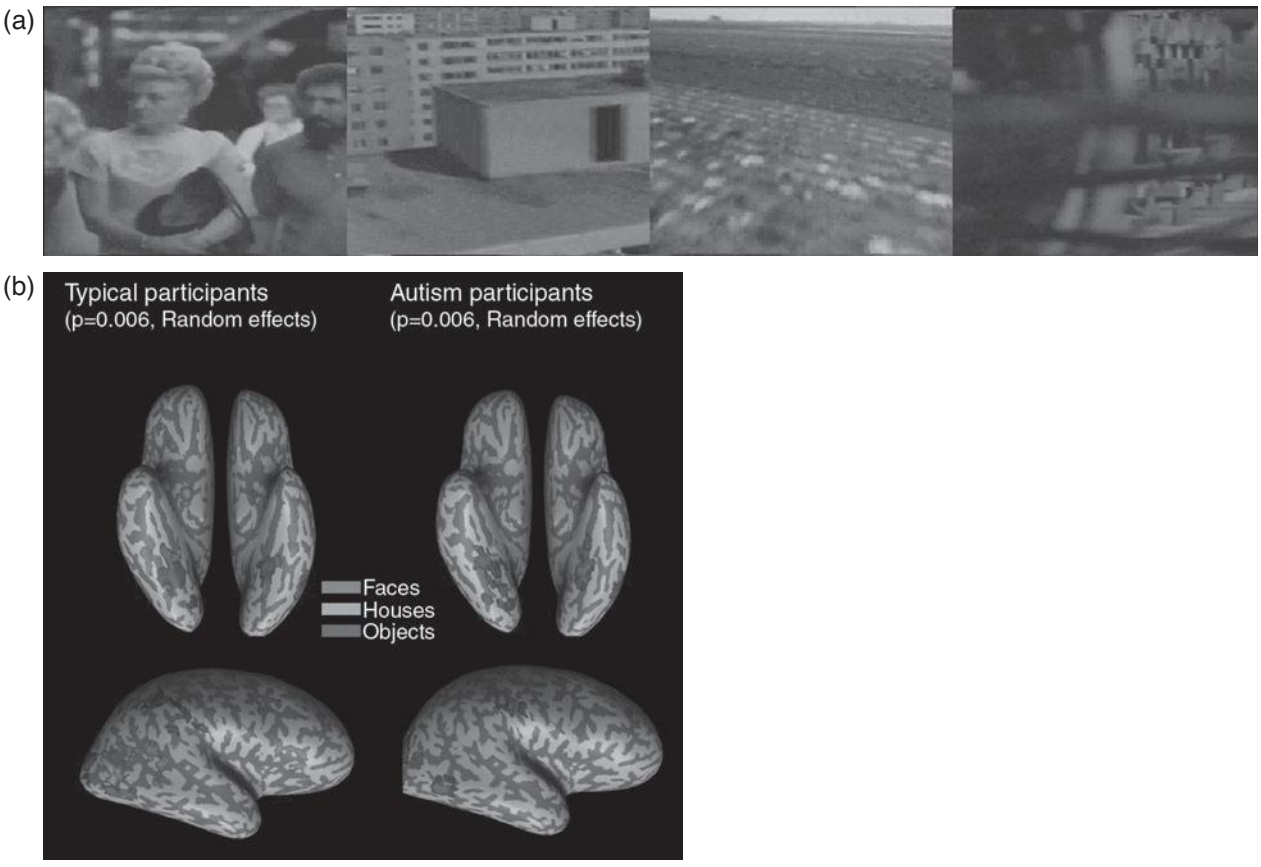

Figure 36–3. Functional MRI study using moving pictures of faces, buildings, scenes, and objects: (a) examples of the stimuli; (b) group averaged cortical maps from the typical and autism groups showing activation in response to faces, buildings, landscapes, and objects. The first map shows the average activation map for typical individuals and the second for individuals with autism. (See Color Plate Section for a color version of this figure.)

reduction in face-related activity in the ASD group and the only face-related activity at this threshold for the autism group is in the right OFA. In contrast, object-related activity in object-related lateral occipital cortex (LO) appears more extensive for the ASD than comparison group, this time in both hemispheres. Ventral visual cortex appears to be organized differently in high-functioning adults with autism, at least for face-selective regions, although subtle differences may also exist for other categories such as objects. These findings are compatible with the other studies that have demonstrated atypical activation in FFA and other face-related regions in ASD and are also compatible with those studies showing enhancement in object related activation (Baily et al., 2005).

Recently, we also evaluated whether functional organization in the ventral visual pathway is fundamentally disrupted in individuals with HFA during adolescence, the important period of visuoperceptual development when HFA individuals fail to develop mature perceptual organizational abilities (Scherf, Luna, Minshew, & Behrmann, 2010). We used the same fMRI paradigm described above to map face-, object-, and place-related activation in 10 high-functioning (FSIQ > 80) adolescents with autism (ages 11–14) and 10 age- and IQ-matched controls. Although the HFA adolescents exhibited typical organization in object- and place-related cortex, as a group they failed to show consistent face-selective activation in classical face regions (FFA, OFA, STS). These results suggest that the functional topography of face-related cortex is selectively disrupted in autism and that this alteration is present in early adolescence, an important stage of cortical specialization for TD adolescents. Furthermore, for those adolescents with autism who do exhibit face-selective activation, face-selective cortex tends to be located in traditionally object-related regions, which supports the hypothesis that perceptual processing of faces in autism may be more akin to the perceptual processing of common objects in typically developing individuals. Such alterations could result from direct pathology to regions within the face-processing network, like the fusiform gyrus (van Kooten et al., 2008), and/or to the structural and functional connections between such regions. Also, alterations in the visual experiences that individuals with autism have with faces as a result of social aversion and/or excessive focus on features may configure these regions in the face-processing network atypically (Grelotti et al., 2005).

Cortical Response Profile Under Naturalistic Conditions

The fMRI studies conducted with ASD individuals, to date, focus predominantly on documenting the cortical response profile of an area or subset of areas of cortex. To examine the claim that multiple higher-order areas, engaged more in integration of information, are more atypical than lower order areas, we have also explored whole brain activation in a group of ASD adults. In perhaps the most naturalistic imaging study we have run to date, we compared the functional connectivity between disparate regions of cortex from data obtained while adults with autism and typical controls lay in a MRI scanner watching a common, popular movie. We mapped the whole-brain activation profile by comparing the evoked fMRI response time courses across different subjects (inter-subject correlation, inter-SC; Hasson et al., 2004). Computing the inter-SC within the typical individuals (typical-typical), on a voxel-by-voxel basis, quantifies the reliability of the response time-courses in each brain area across members of the typical group. Recently, using this technique, Hasson et al. (2009) demonstrated that, across typical observers, approximately 30–65% of the cerebrum evinces similar shared reliable response time-courses under free-viewing of complex naturalistic stimuli, and this provides a benchmark against which to assess the inter-SC in ASD. Computing the inter-SC between the typical and the autism groups (typical-autism) provides a measure of similarity in the functional response in each brain areas across the two groups. Low inter-SC between the typical-autism group in conjunction with high inter-SC within the typical group would indicate that the response time course in a given brain area is markedly different in individuals with autism from that of the typical individuals. Moreover, computing the inter-SC within the autism group (autism-autism) alone can identify reliable response time courses, which are unique to the ASD group and are not observed in the typical subjects.

All participants watched a 10-minute excerpt from the popular movie, *The Good, the Bad, and the Ugly,* directed by Sergio Leone, and answered questions posed afterward to probe their comprehension of the plot and sequence of events. After normalizing all brains to the Talairach coordinate system, we calculated the inter-SC across the entire movie sequence within the typical group on a voxel-by-voxel basis (see Hasson et al., 2004; Hasson et al., 2009, for more details). This was done separately for every voxel. Figure 36-4A shows the activation profile sampled from the vicinity of the calcarine sulcus, which includes the primary visual cortex and nearby early visual areas (termed in the paper as area V1+) for each individual in each group, plotted across the entire movie sequence (600s). We also show the correlation among the typical individuals (0.32), reflecting strong similarity in the individual time courses, and among the ASD individuals (0.14), reflecting rather different time courses in each individual. This area was chosen as a clear illustrative example of the findings, but similar results were obtained in the other regions of cortex (see Figure 36-4D). In sum, the response time-courses in area V1+ were highly reliable across all typical subjects whereas the time-courses from the same area in the individuals with autism, although highly fluctuating, were poorly correlated across individuals.

The reduction in the correlation of the response time courses in individuals with autism held across large regions of posterior cortex. Figure 36-4D presents the average inter-SC values for the within- and between-group comparisons across the preselected ROIs. The high correlation values within the group of control subjects (typical-typical: red) replicate previous findings (Hasson et al., 2004). In all ROIs (including early and higher-order regions), the autism-autism analysis (dark green) and the autism-control analysis (light green) showed a substantially reduced correlation of about 40–50%,

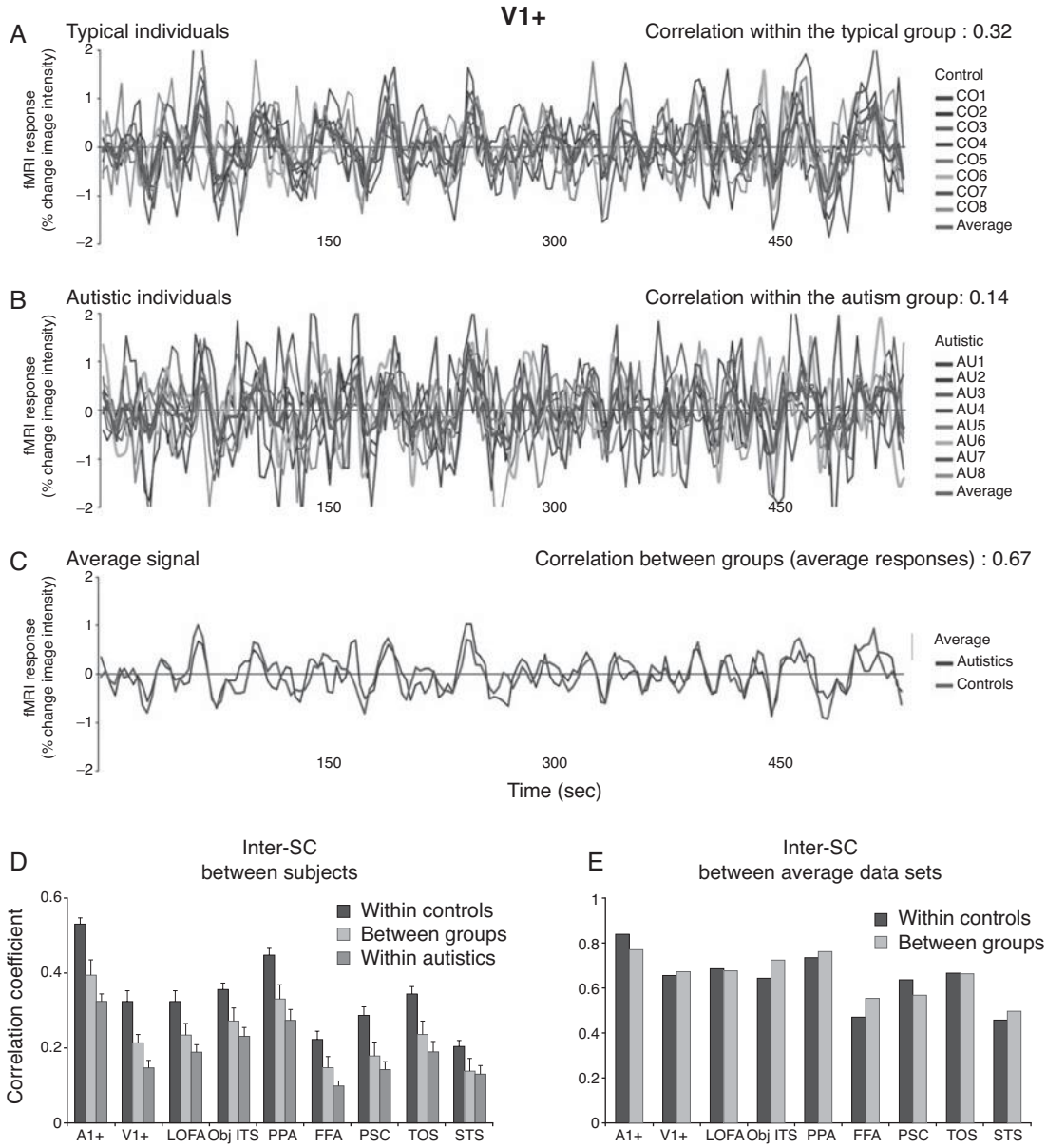

Figure 36–4. Signal fluctuations within ROIs. Visual cortex (V11) response time courses for (A) each typical subject and (B) each participant with autism. (C) The average signal for the typical group (red line) and autism (blue line) group. (D) The mean inter-SC values for the within-typical group (typical–typical, red bars), within-autism group (autism–autism, light green bars), and between the two groups (autism–typical, green bars) for selected ROIs. ROI abbreviations: A11, primary and secondary auditory cortices; V11, primary and secondary visual cortices; LOFA, lateral occipital cortex responsive to pictures of faces; Obj-ITS, object-related area in the inferior temporal sulcus; PPA, parahippocampal place area; FFA, fusiform face area; PCS, posterior central sulcus responsive to pictures of objects; TOS, transverse occipital sulcus responsive to pictures of places; STS-Face, area in superior temporal sulcus responsive to pictures of faces. (E) The inter-SC between the average autism–typical time courses (green bars) and the typical–typical time courses (red bars) in each ROI (same abbreviations as in D). Note the extent of variability in signal fluctuation in the autism individuals relative to the typical subjects. Moreover, note that by averaging the time courses within a group the responses become highly correlated across groups. (See Color Plate Section for a color version of this figure.)

relative to the typical subjects' inter-SC values. An important observation, however, is that the overall inter-SC values are higher in primary sensory cortices than in higher-order association cortex, consistent with the hypothesis that more primary regions of cortex, whose responsibility it is to mediate more simple forms of processing, might be better preserved in ASD than those regions whose role it is to integrate the higher-order statistics of the more complex input.

Visual Processing: Conclusions

Taken together, our investigations into the psychological and neural mechanisms of visual processing in high-functioning individuals with ASD reveal a similar pattern: there is relative preservation (and perhaps even enhancement, on some accounts) in more elemental, simple, or featural processing, whereas information processing that requires the integration

of the simple elements is disproportionately affected. The imaging data yield a similar profile: relative preservation of earlier parts of the visual system and more pronounced atypical activation in higher-order regions. These alterations, while appearing subtle, nonetheless have a profound impact on how the brain in autism processes information, and, in turn, how individuals with autism "see" the world differently (Behrmann, Thomas, & Humphreys, 2006).

These findings exemplify some of the major advances that have occurred in delineating the neurobiological basis of neuropsychological functioning in autism in the past decade in large part due to the impact of numerous, carefully executed functional MRI studies in conjunction with equally meticulous cognitive studies. These findings have created a convergent and consistent picture of distinctive alterations in cortical functional connectivity in ASD characterized by intact and or increased local connectivity in posterior or occipital parietal regions (and probably other primary cortical regions too) and decreased systems connectivity that particularly impacts connectivity with frontal cortex. This distinctive alteration in circuitry has been shown to alter how the brain processes a broad range of social and nonsocial information, how the person with ASD perceives the world, and how the person with ASD thinks and feels.

General Conclusions

Across all domains impacted by autism, the common thread is the preservation of elementary skills and greatest impairments in those abilities that require on-line integration of information. In previous decades, this dissociation was characterized as a contrast between intact visuospatial abilities and impaired verbal abilities, which was considered nearly pathognomonic of autism. With technologic advances, this pattern is now understood in terms of selective disturbances in cortical connectivity. Recent genetic advances have identified a multitude of abnormal and mutated genes for ASD that all share a role in the development of neuronal connections and share common molecular signaling pathways. A little is known about the molecular pathophysiology of ASD but far from enough to explain the specific connection of these genes to the impact ASD has on cortical circuitry. These findings have produced a convergent developmental neurobiological model of autism as a disorder of neuronal organization and in some cases neuronal migration as well as the first neurobiologically based treatment for prevention of syndromic autism.

Challenges and Future Directions

- In the next 5 years, our hope is that investigators will work to advance the knowledge in their respective areas to diminish the gaps and increase the specificity of detail essential to designing treatments for autism.
- The focus on future work should strive to explain autism as a developmental neurobiological disorder with disturbances in cortical circuitry to create an integrated, multidimensional definition of the cause of autism from gene to behavioral variability.
- Interdisciplinary research that seeks to integrate and correlate genetic, neurobiological, neurological, and behavioral findings will be crucial for making progress in understanding the etiology, brain basis, and effective treatments for the complex disorder of ASD.

SUGGESTED READINGS

Minshew, N. J., Goldstein, G., & Siegel, D. J. (1997). Neuropsychologic functioning in autism: Profile of a complex information processing disorder. *Journal of the International Neuropsychological Society*, *3*, 303–316.

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