Autism: A Window Onto the Development of the Social and the Analytic Brain

Simon Baron-Cohen and Matthew K. Belmonte

Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, CB2 2AH, United Kingdom; email: sb205@cam.ac.uk, belmonte@mit.edu

Key Words

social cognition, attention, frontal lobe, network connectivity

Abstract

Although the neurobiological understanding of autism has been increasing exponentially, the diagnosis of autism spectrum conditions still rests entirely on behavioral criteria. Autism is therefore most productively approached using a combination of biological and psychological theory. The triad of behavioral abnormalities in social function, communication, and restricted and repetitive behaviors and interests can be explained psychologically by an impaired capacity for empathizing, or modeling the mental states governing the behavior of people, along with a superior capacity for systemizing, or inferring the rules governing the behavior of objects. This empathizing-systemizing theory explains other psychological models such as impairments of executive function or central coherence, and may have a neurobiological basis in abnormally low activity of brain regions subserving social cognition, along with abnormally high activity of regions subserving lower-level, perceptual processing—a pattern that may result from a skewed balance of local versus long-range functional connectivity.

Contents

INTRODUCTION

Autism is diagnosed when a child or adult has abnormalities in a triad of behavioral domains: social development, communication, and repetitive behaviors and obsessive interests (Am. Psychol. Assoc. 1994, World Health Organ. 1994). Autism can occur at any point on the intelligence quotient (IQ) continuum, and IQ (Rutter 1978) and level of language function by age six (Szatmari et al. 2003) are strong predictors of clinical outcome. Whereas autism *per se* is invariably accompanied by language delay, people with Asperger syndrome (AS) share with autism the social impairments and restricted behaviors, but without serious language impairment, and with verbal and nonverbal IQ in the average range or above (Wing 1981). This review introduces the main cognitive theories of autism and relates these theories to key neurobiological findings.

EMPATHIZING AND SYSTEMIZING

The empathizing-systemizing theory of autism (Baron-Cohen 2002) proposes that autism spectrum conditions involve deficits in the normal process of empathy, relative to mental age. These deficits can occur by degrees. The term empathizing encompasses a range of other terms: theory of mind, mind-reading, empathy, and taking the intentional stance (Dennett 1987). Empathy comprises two major elements: (*a*) attribution of mental states to oneself and others, as a natural way to make sense of the actions of agents (Baron-Cohen 1994, Leslie 1995, Premack 1990); and (*b*) emotional reactions that are appropriate to others' mental states.

Since the first test of mind-blindness was administered to children with autism (Baron-Cohen et al. 1985), more than thirty experimental tests have been developed. The vast majority of these tests have revealed profound impairments in the development of empathizing (Baron-Cohen 1995, Baron-Cohen et al. 1993). The residual effects of such impairments can be subtle but nevertheless significant; some children and adults with AS, for example, perform at ceiling on simple tests of inference of others' beliefs but are impaired at inferring others' complex emotions (Baron-Cohen et al. 2001). This deficit in empathizing is thought to underlie the difficulties that such children experience in social and communicative development (Baron-Cohen 1988, Tager-Flusberg 1993), and in the imagination of others' minds (Baron-Cohen 1987, Leslie 1987). We can think of these symptoms as the triad of deficits.

Although autism is most often conceptualized as a syndrome of deficits, its altered developmental emphases can also lead to remarkable cognitive strengths. The pattern of cognitive superiorities found in autism can be explained by the concept of systemizing: the drive to analyze objects and events to understand their structure and to predict their future behavior. Systems are ubiquitous in the environment: technical systems (such as machines and tools), natural systems (such as biological and geographical phenomena), and abstract systems (such as mathematics or computer programs). We make sense of such

systems by observing the regularities in their behavior and inferring the rules that govern the system via an analysis of input-operation-output relationships (Baron-Cohen 2002). The empathizing-systemizing (E-S) theory holds that alongside deficits in empathizing, in autism systemizing is either intact or superior (Baron-Cohen et al. 2002). Several studies indicate that systemizing in autism is at least in line with mental age, or superior (Baron-Cohen et al. 1986, 2003; Lawson et al. 2004). Systemizing may underlie a different set of behavioral features in autism that we refer to as the triad of strengths (**Figure 1**).

EXECUTIVE FUNCTION

People with autism spectrum conditions show unusually strong repetitive behaviors, a desire for routines, and a need for sameness. One cognitive account of this aspect of the syndrome is the executive dysfunction theory (Ozonoff et al. 1991), which posits that autism involves a form of frontal lobe pathology leading to perseveration or inability to shift focus. Although evidence for such executive deficits does exist (Pennington et al. 1997, Russell 1997), the high variance in measures of executive function in autism spectrum conditions (Liss et al. 2001), along with the lack of correlation between measures of executive function and measures of reciprocal social interaction and repetitive behaviors (Joseph & Tager-Flusberg 2004), suggests that executive dysfunction is unlikely to be a core feature of autism spectrum conditions.

The executive account has also traditionally ignored the content of repetitive behaviors. The E-S theory in contrast draws attention to the fact that much repetitive behavior involves the child's obsessional or strong interests, the foci of which cluster in the domain of strongly regular systems (Baron-Cohen & Wheelwright 1999). Rather than primary executive dysfunction, these behaviors may reflect an unusually strong interest in systems.

Figure 1
Complementary triads of deficits and strengths in autism.
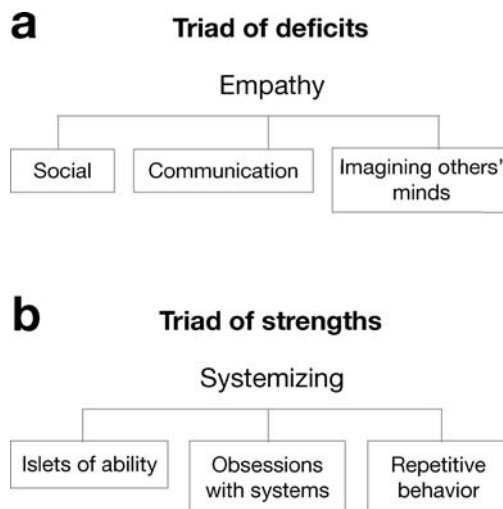
CENTRAL COHERENCE

The concept of weak central coherence (CC) (Frith 1989, Happé 1996) refers to an abnormally weak tendency to bind local details into global percepts. Weak central coherence in autism has been demonstrated in the context of superior performance on visuomotor tasks such as the Embedded Figures Test (EFT) (Jolliffe & Baron-Cohen 1997, Shah & Frith 1983), the Wechsler Block Design subtest (Shah & Frith 1993), tasks of visual discrimination (Plaisted et al. 1998a) and visual search (Plaisted et al. 1998b, O'Riordan et al. 2001), as well as impaired performance on more abstract tasks such as arranging sentences to form a coherent context (Jolliffe & Baron-Cohen 2000). The general pattern is one of stronger-than-normal segmentation of stimuli and attention to detail within stimuli.

The CC theory thus predicts that people with autism spectrum conditions will perform best on (and, by implication, will be most driven by) tasks and occupations in which piecemeal analysis of individual details is an asset, whereas the E-S theory predicts that people with autism spectrum conditions will be most driven by tasks and occupations that involve analysis of rule-based systems. To a great extent, these predictions overlap:

Systemizing demands excellent attention to detail to isolate parameters that may then be tested individually for their effects on the system's output.

However, differences in theoretical predictions arise when one considers the case of complex systems in which manipulations of inputs produce widespread effects on outputs, or in which differences in outputs are evoked by complex interactions among widely separated inputs. The CC theory, taken by itself, predicts that people with autism will fail to learn such systems because mastering them requires a global view of the interrelations between large sets of inputs and outputs, as opposed to simple systems that can be understood in terms of relations between one or a few inputs and outputs. Conversely the E-S theory, taken by itself, predicts that (relative to their mental age) people with autism will be able to learn how any sort of regular system works, regardless of its complexity, so long as it is highly lawful.

A third prediction arises, though, if one considers E-S and CC not as mutually exclusive explanations of autistic behavior, but as complementary ones that can be developmentally unified. Specifically, the attention to detail described by weak central coherence may be one of the earliest manifestations of a strong drive toward systemizing, or vice versa, interest in systemizing may arise as a consequence of attention to detail. As cognitive capacities mature, strong "systemizers" may begin to apply a sort of engineering methodology, in which even complex systems are understood by successive local observations in which one input at a time is manipulated while all others are held constant, and effects on the outputs are observed in a similarly sequential manner. Thus the ultimate effect of the cognitive style described as weak central coherence may be, at least in high-functioning cases of autism, not a lack of ability to understand global relationships but rather a difference in the process by which global relationships are established. Experimental comparison of the ability to make inferences about complex systems, between people with and without autism spectrum conditions and across different stages of development or levels of functioning, may lead to the recognition of E-S as an elaboration of the CC model, one that may make more precise and more accurate predictions about the behavior of people with autism when confronted with complex systems.

Although both central coherence and systemizing are useful psychological models to explain many aspects of autistic behavior, a complete explanation of autism will require that these psychological models be joined with neurobiological substrates—a process complicated by the fact that neither capacity is likely to be atomic in neurobiological terms.

THE SOCIAL BRAIN

A neural basis of empathy has built on a model first proposed by Brothers (1990). She suggested, on the basis of animal lesion studies (Kling & Brothers 1992), single-cell recording studies (Brothers et al. 1990), and neurological studies, that social intelligence was a function of three regions: the amygdala, orbitofrontal and medial frontal cortices, and superior temporal sulcus and gyrus. Together, she termed these interacting regions the social brain (**Figure 2**). It is perhaps no coincidence that abnormalities in autism have been found in the amygdala, in orbito-frontal cortex, and in medial frontal cortex.

Four lines of evidence converge on the hypothesis of an amygdala deficit in autism (Baron-Cohen et al. 2000). Histopathologically, cell packing density in the amygdala is increased in autism (Bauman & Kemper 1985, 1994). Behaviorally, people with autism show a similar pattern of deficits to those seen in patients with amygdala lesions (Adolphs et al. 2001, Howard et al. 2000). In terms of gross anatomy, magnetic resonance imaging (MRI) morphometry suggests abnormal volume of the amygdala, although there is disagreement as to whether amygdala volume in autism may be reduced (Abell et al. 1999, Aylward et al.
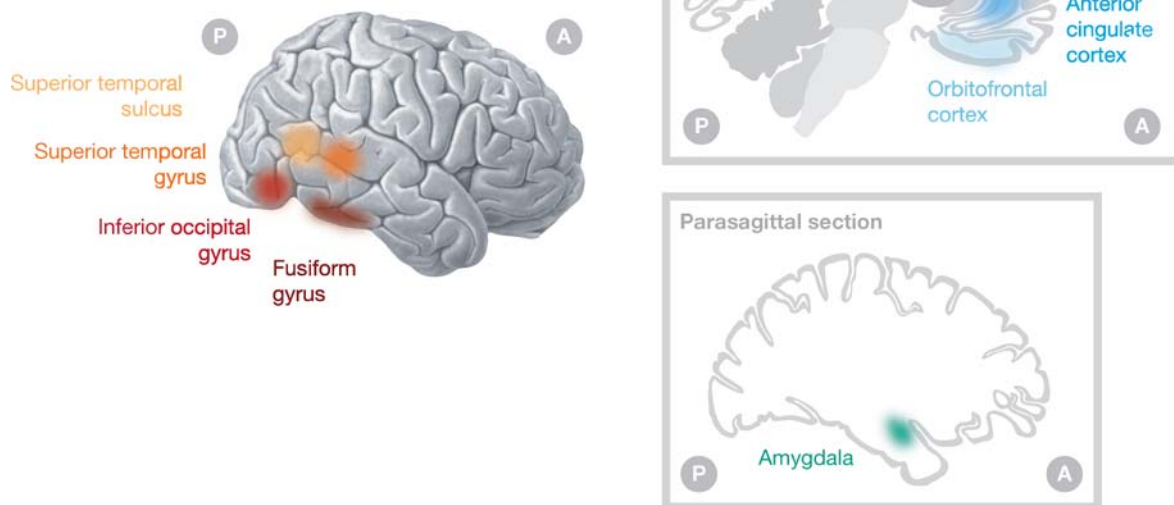
Figure 2

The social brain. Medial and inferior frontal and superior temporal cortices, along with the amygdala, form a network of brain regions that implement computations relevant to social processes. Perceptual inputs to these social computations may arise in part from regions in the fusiform gyrus and from the adjacent inferior occipital gyrus that activate in response to faces. This social computational network has been implicated in autism. (Adapted from Talairach & Tournoux 1998 and from an illustration by C. Ashwin.)

1999, Pierce et al. 2001) or enlarged (Howard et al. 2000, Sparks et al. 2002). Physiologically, adults with autism spectrum conditions manifest abnormally low activation of the amygdala during tasks of inferring emotion from pictures of the eyes (Baron-Cohen et al. 1999) or of the whole face (Wang et al. 2004), and during passive processing of facial expressions of unfamiliar faces (Critchley et al. 2000, Pierce et al. 2001) but not familiar faces (Pierce et al. 2004). In other areas of the social brain, reduced activity has been found in left medial frontal cortex during an empathizing (theory of mind) task (Happé et al. 1996), in orbitofrontal cortex during recognition of mental state words (Baron-Cohen et al. 1994), and in superior temporal sulcus during

passive listening to speech sounds as compared with nonspeech sounds (Gervais et al. 2004).

AUTISM AS A DEVELOPMENTAL END POINT

These studies of the social brain have shown that by the time the autistic brain is fully developed, key processes and structures associated with social cognition are abnormal. Though this correspondence between abnormal brain function and behavioral impairments may seem a compelling basis for a neurobiological theory of autism as a deficit of empathizing, in the analysis of developmental conditions it is crucial to realize

that the symptoms that are most diagnostically significant and clinically debilitating are not necessarily the most etiologically primary (Belmonte 2004a). Primary dysfunctions can be masked by the evolution of compensatory processing strategies that normalize behavior (Rubia 2002), and also by the induction of activity-dependent secondary dysfunctions (Akshoomoff et al. 2002, Courchesne et al. 1994a), which disrupt behavior in new ways.

A tacit assumption in almost all functional imaging studies, historically, has been that the behavioral or cognitive capacity of interest can be localized to one or a few discrete brain structures, just as clinical impairments in cases of acquired brain disorders can be associated with anatomically circumscribed lesions. Although this lesion model is experimentally convenient, it is likely to be inappropriate to the study of developmental conditions in which dysfunctions are likely to comprise not single regions but complex networks of anatomically and functionally distant areas (Johnson et al. 2002). Localized abnormalities therefore may provide some insight into developmental end points but not directly into developmental processes. The eventual understanding of autism will hinge on our accepting the classification "developmental disorder" as one of not merely taxonomic but also etiologic significance.

THE ANALYTICAL BRAIN

A more complete picture of brain function and dysfunction in autism can be constructed if one examines not only the deficits associated with impaired empathizing but also the more subtle cognitive differences and even superiorities associated with strong systemizing. For instance, functional imaging during performance of the Embedded Figures Test—on which behavioral performance of people with autism is superior to normal—reveals unusually high activation in ventral occipital areas and abnormally low activation in prefrontal and parietal areas (Ring et al. 1999).

This theme of abnormally high activation in unimodal or low-level processing regions alongside low activation in frontal and other integrative regions (**Figure 3**) recurs in findings of heightened activity during face processing in peristriate cortex (Critchley et al. 2000), inferior temporal gyrus (Schultz et al. 2000), medial occipital gyrus and superior parietal lobule (Hubl et al. 2003), precuneus (Wang et al. 2004), and other areas outside the fusiform face area (Pierce et al. 2001); by comparison, fusiform activity is abnormally low. Similarly, a visual attention task evokes heightened activity in ventral occipital cortex and abnormally low activations in parietal and prefrontal cortices (Belmonte & Yurgelun-Todd 2003). In a sentence processing task, activation is greater than normal in Wernicke's area and less than normal in Broca's area, which suggests that processing is enhanced at the level of single words and impoverished at the level of sentential context (Just et al. 2004). In addition, activity in superior temporal gyrus during inference of mental state from pictures of eyes is heightened (Baron-Cohen et al. 1999), and connectivity between extrastriate and prefrontal and temporal cortices during attribution of mental states from movements of animated shapes is weakened (Castelli et al. 2002), while prefrontal and medial temporal activations are abnormally low. Cardiovascular, neuroendocrine, and neurochemical indices of arousal in novel and stressful situations are consistent with this idea of abnormal excitability or arousal (Hirstein et al. 2001, Tordjman et al. 1997).

Perhaps as a consequence of such high excitability in response to both relevant and irrelevant stimuli, neural response as a function of selective attention is abnormally modulated. In adults with autism, the P1 evoked potential is either abnormally augmented in response to stimuli at the attended location, or abnormally generalized to stimuli distant from the attended location (Townsend & Courchesne 1994). During shifts of attention between hemifields, the normal, spatiotopically selective augmentation of the

visual steady-state evoked potential is absent, and instead both hemispheres activate indiscriminately during shifts of attention into either hemifield (Belmonte 2000, Belmonte & Yurgelun-Todd 2003). In children with autism, the visual N2 to novel stimuli is augmented during task performance, even when these stimuli are not relevant to the task (Kemner et al. 1994). When a response is required to an auditory stimulus, the P3 in these same children with autism is reported to be abnormally generalized to occipital sites overlying visual processing areas (Kemner et al. 1995). In general, both in children and in adults, perceptual filtering in autism seems to occur in an all-or-none manner; there is little specificity in selecting for the location of the stimulus, for the behavioral relevance of the stimulus, or even for the sensory modality in which the stimulus appears. Although

compensatory cognitive mechanisms may substitute for this neural inefficiency during periods when attention is statically focused (Belmonte & Yurgelun-Todd 2003), such mechanisms may be unable to update quickly,

Figure 3

High activation at low levels of processing and low activation at high levels of processing in the autistic brain. (*a*) This functional magnetic resonance image in a parasagittal plane through the right hemisphere ($x = 13$) illustrates hyperactivation in intraparietal sulcus and hypoactivation in middle frontal gyrus in children with autism spectrum disorders, as compared with normal children performing a difficult visual discrimination task (M.K. Belmonte, M. Gomot & S. Baron-Cohen, unpublished data). Simultaneously attending to the centers of two 3×3 arrays of oriented, colored sine-wave gratings, one in the left hemifield and one in the right hemifield, subjects indicated via a forced-choice response whether a target orientation was present in the central stimulus in one hemifield along with a target color in the central stimulus in the other hemifield, while ignoring the surrounding distractors. Stimuli were presented for 167 ms, with a 3 s response period. The functional correlation compares event-related activity when distractors are incongruent to the attended stimuli with event-related activity when distractors are congruent. (*b*) This axial slice ($z = +18$) illustrates abnormally low functional correlations between anterior cingulate cortex [approximate Talairach coordinates (0, 40, 0), not shown on this slice] and bilateral anterior superior temporal gyri in the autism group.
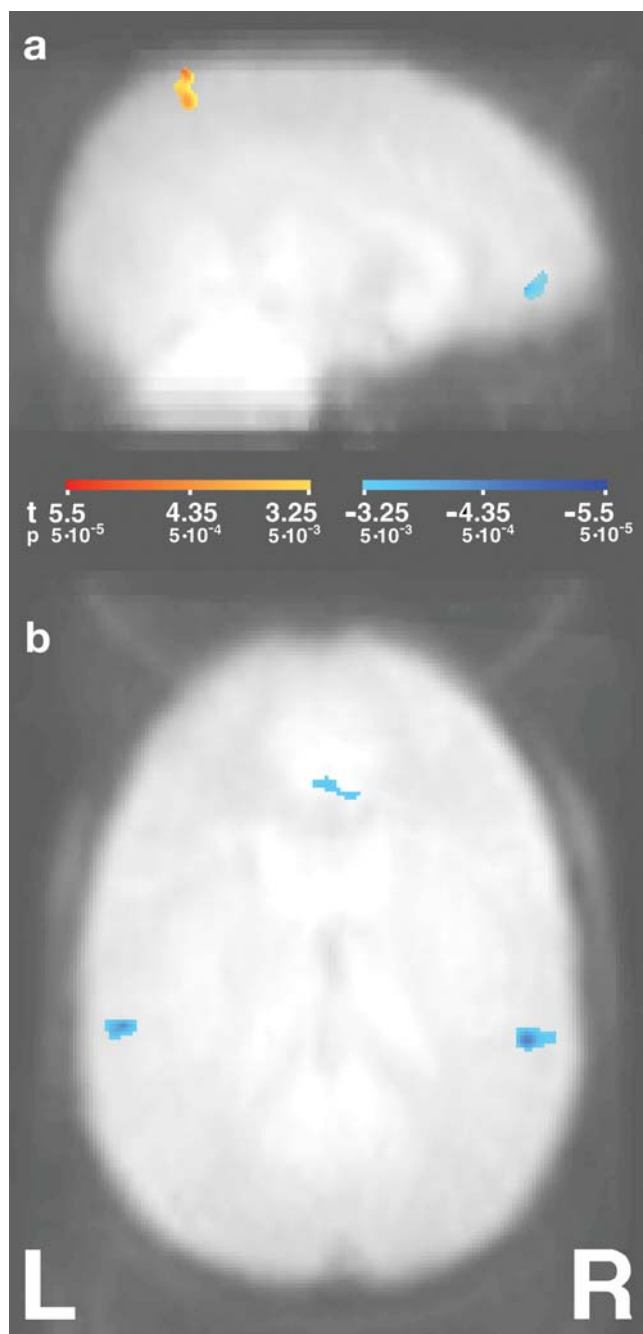
leading to the behavioral symptom of impairment in rapid shifts of attention between modalities (Courchesne et al. 1994b), between spatial locations (Belmonte 2000; Harris et al. 1999; Townsend et al. 1996a,b, 1999; Wainwright-Sharp & Bryson 1993, 1996), and between object features (Courchesne et al. 1994c, Rinehart et al. 2001).

One should consider the possible developmental relationship between abnormal attention and perception in autism and the diagnostic feature of restricted and repetitive behaviors. Normal perception can be thought of as viewing a film in a sort of Cartesian cinema: As the actors and events in the film convey information in multiple modalities and at multiple locations on the screen, the viewer integrates these sources rapidly and effortlessly. If, however, neural properties preclude shifting attention among these many foci and integrating information analyzed by various perceptual and cognitive subsystems, the mind's ability to construct an internal narration of the film's events will be impaired. Consider trying to make sense of a film from only the audio track or only a small corner of the picture.

To make matters worse, films in the Cartesian cinema normally have very short runs because the events and experiences of every day and every hour are unique. A natural response when faced with this difficulty in integrating external events into coherent internal representations would be to replay the same film over and over again, in hopes that over many screenings one will be able to piece together all the details. Considered in the context of abnormal attention and perception, reliance on restricted and repetitive behaviors may thus be an adaptive mechanism (Belmonte et al. 2004b), a way of decreasing environmental variance so that the social world can be reduced more effectively to a regular, predictable, and systemizable set of scripts. Excessive repetition or "need for sameness" may be a sign of hypersystemizing (Baron-Cohen 2004). In this regard, some of the complex behavioral abnormalities in autism

can be viewed as the developmental reaction to an atypical perceptual and cognitive style.

A BASIS IN NEURAL CONNECTIVITY

The combination of sensory hyperarousal and abnormal attentional selectivity suggests that autism may involve overconnected neural networks, in which signal is insufficiently differentiated from noise or irrelevant information and in which information capacity is therefore reduced (Belmonte et al. 2004a,b; Rubenstein & Merzenich 2003). This idea is consistent with genetic and neurochemical results, such as linkage to the 15q11–13 region, which contains a cluster of γ-amino-butyric acid (GABA) receptor genes (Buxbaum et al. 2002), low GABA receptor binding in hippocampus (Blatt et al. 2001), and low GABA levels in blood platelets (Rolf et al. 1993), and with the substantial comorbidity of epilepsy with autism (Ballaban-Gil & Tuchman 2000). In addition, high levels of noise in neural networks could explain autistic psychophysical anomalies such as high visual motion coherence thresholds (Milne et al. 2002) and broad tuning of auditory filters (Plaisted et al. 2003). Photomicrographic examination of neurons in several cortical regions suggests a reduction in the size of cortical minicolumns in the autistic brain and an increase in cell dispersion within minicolumns (Casanova et al. 2002a,b)—characteristics that could alter local network properties along with long-range projections (Courchesne & Pierce 2005). Magnetic resonance spectrographic findings of reduced N-acetyl aspartate and other neuronal metabolites (Chugani et al. 1999, Otsuka et al. 1999, Hisaoka et al. 2001, Friedman et al. 2003) are consistent with this finding of more widely dispersed neurons.

This notion of abnormally high neural connectivity in autism seems inconsistent with functional imaging results showing low correlations between levels of activation in widely separated brain regions (Castelli et al. 2002, Just et al. 2004). Indeed, some

investigators have proposed that autism involves not a surfeit of connectivity but rather a deficit (Brock et al. 2002, Just et al. 2004)—a dysfunction that would explain and unify psychological theories of deficits in executive function (Ozonoff et al. 1991), complex information processing (Minshew et al. 1997), central coherence (Frith 1989), and empathizing (Baron-Cohen et al. 2002), all of which depend on the rapid and integrated operation of many separate neural systems.

The apparent contradiction between theories of overconnectivity and underconnectivity in autism may arise because of the multiple connotations of the term connectivity. Conceptually we can differentiate local connectivity within neural assemblies from long-range connectivity between functional brain regions. On another axis, we can also separate physical connectivity (associated with synapses and tracts) from computational connectivity (associated with information transfer). Physically, in the autistic brain, high local connectivity may develop in tandem with low long-range connectivity (Just et al. 2004, Belmonte et al. 2004a, Courchesne & Pierce 2005)—perhaps as a consequence of widespread alterations in synapse elimination and/or formation that skew the computationally optimal balance between local and long-range connections (Sporns et al. 2000). A decrease in network entropy due to indiscriminately high connectivity within local networks could yield abnormally low information capacity and may develop in tandem with abnormally low computational connectivity with other regions.

ABNORMAL EARLY BRAIN DEVELOPMENT

How can this hypothesis of abnormally high local connectivity and abnormally low long-range connectivity be tested? Certainly, a large amount of information is likely to be found eventually in large-scale histopathological studies of the autistic brain across many brain regions and developmental periods. Until such detailed microscopic data are available, investigation can be guided by in vivo imaging studies. Both MRI volumetric analysis and simple measures of head circumference indicate that autism involves transient postnatal macrencephaly (Courchesne 2002, Courchesne et al. 2003). Neonates later diagnosed with autism or PDD-NOS (pervasive developmental disorder—not otherwise specified) have normal head circumference; but by 2–4 years of age, 90% of these have larger-than-average brain volumes (Aylward et al. 2002, Carper & Courchesne 2000, Courchesne et al. 2001, Piven et al. 1995, Sparks et al. 2002).

This enlargement occurs specifically within cerebellar and cerebral white matter and cerebral gray matter (Courchesne et al. 2001, Herbert et al. 2003). Anatomical parcellation of white matter reveals that the enlargement occurs in short-range, radiate fibers but not in deeper, long-range fibers (Herbert et al. 2004). Indeed, the posterior corpus callosum in autism is actually smaller than normal (Egaas et al. 1995), and the degree of this callosal hypoplasia correlates with the degree of frontal hyperplasia (Lewis et al. 2004). This compartmental specificity of white matter hyperplasia is consistent with the idea of differential effects on local and long-range connections. Regionally, frontal lobes show the greatest degree of enlargement, and occipital lobes show the least (Carper et al. 2002, Piven 2004); within the frontal lobe, the dorsolateral convexity and medial frontal gyrus—areas that figure prominently in the social brain—show significant overgrowth, whereas precentral gyrus and orbital cortex are not robustly affected (Carper & Courchesne 2005). Thus the cortical areas most affected are precisely those broadly projecting, phylogenetically and ontogenetically late-developing regions that are essential to complex cognitive functions such as social behavior and language. This frontal emphasis in the pattern of overgrowth seems to be the likely cause of anterior and superior shifting of major sulci in the frontal

AS: Asperger syndrome

CC: central coherence

E-S: empathizing-systemizing

EEG: electroen-cephalogram

GABA: γ-amino-butyric acid

PDD-NOS: Pervasive Developmental Disorder—Not Otherwise Specified

and temporal lobes in autism (Levitt et al. 2003). Cerebellar and cerebral white matter volumes, combined with cerebellar vermis size, can discriminate 95% of toddlers with autism from normal controls and can predict whether a child with autism will be high or low functioning (Courchesne et al. 2001).

Anatomical findings outside the cerebrum also may bear on the issue of connectivity. The cerebellum, in particular, is one of the most consistently abnormal structures in the autistic brain (Courchesne 1997, Hashimoto et al. 1995). The number of Purkinje cells in cerebellar cortex is abnormally low (Bauman & Kemper 1985, 1994; Ritvo et al. 1986; Williams et al. 1980). Purkinje cells are the sole inhibitory influence on the deep cerebellar nuclei, which project via the thalamus to most of the cerebral cortex. Absence of Purkinje cell output could therefore induce abnormal excitability in cerebro-ponto-cerebellar-thalamic control loops (Courchesne 1997), increasing the level of noise in cortical networks. Interestingly, people with autism show abnormally low activation of cerebellar cortex in a visual vigilance task (Allen & Courchesne 2003), but abnormally high activation during a purely motor task of self-paced button-pressing (Allen et al. 2004, Allen & Courchesne 2003), and the degree of abnormally high cerebellar motor activation correlates with the anatomical deficit in cerebellar volume (Allen et al. 2004).

GENETICS AND THE BROADER AUTISM PHENOTYPE

Ultimately the cognitive and neural abnormalities in autism spectrum conditions are likely to be due to genetic factors. The sibling recurrence risk for autism is approximately 4.5%, or a tenfold increase over general population rates (Jorde et al. 1991). An epidemiologic study of same-sex autistic twins found that 60% of monozygotic pairs were concordant for autism versus 0% of dizygotic pairs (Bailey et al. 1995).

When a broader phenotype (of related cognitive or social abnormalities) was considered, 92% of monozygotic pairs were concordant versus 10% of dizygotic pairs. The high concordance in monozygotic twins indicates a high degree of genetic influence, and the risk to a monozygotic co-twin can be estimated at more than 200 times the general population rate. The cognitive profile in siblings of people with autism includes superior spatial and verbal span, poor set-shifting, poor planning, and poor verbal fluency (Hughes et al. 1999). Parents of children with autism spectrum conditions perform above normal on the Embedded Figures Test (Baron-Cohen & Hammer 1997) and other tasks that demand strong systemizing skills (Happé et al. 2001), but they perform below normal when inferring mental state from facial expression (Baron-Cohen & Hammer 1997), a task that requires empathizing. In addition, parents show impairments in pragmatic language (Folstein et al. 1999) and executive function (Hughes et al. 1997) and display autistic personality characteristics such as rigidity, aloofness, and anxiety (Piven et al. 1997). In many first-degree relatives, performance IQ is lower than verbal IQ (Folstein et al. 1999, Fombonne et al. 1997, Piven & Palmer 1997) owing to impairment on Picture Arrangement and Picture Completion, both of which demand attention to global, contextual information.

These subtle characteristics of the broader autism phenotype are visible in the systemizing skills that relatives tend to develop: Occupations in engineering are overrepresented in the fathers and grandfathers of people with autism (Baron-Cohen et al. 1997), and conversely, the incidence of autism is increased in the families of engineers, mathematicians, and physicists (Baron-Cohen et al. 1998). These subtle abnormalities in nonautistic family members may be particularly informative as to the etiology of autism because they may represent primary differences that have not been masked by the full syndrome of autism (Belmonte et al. 2004b).

Although investigators have not yet agreed on the genetic loci involved in autism, two regions stand out in several (but not all) studies. These are 15q11–13, near the GABA$_A$ß$_3$ receptor subunit gene (*GABRB3*), and 17q11.2, near the serotonin transporter gene (*SLC6A4*). The latter is of interest because of reports of elevated serotonin (5HT) levels of platelets in autism (Anderson 1990). Serotonin innervates the limbic system and so plausibly plays a role in emotion recognition and empathy. In mice, mothers homozygous for *GABRB3* knockout fail to engage in normal nurturing behavior and have epileptiform electroencephalograms (EEG) (Homanics et al. 1997, DeLorey et al. 1998), suggesting abnormal cortical excitability. A recent association of autism with the X-linked neuroligin genes *NLGN3* and *NLGN4* (Jamain et al. 2003) is consistent with the notion of abnormal neural connectivity, as well as potentially helping to explain the 4:1 ratio of males to females affected by autism. Immunogenetic and immunological abnormalities and infectious etiologies in autism (van Gent et al. 1997) are another domain likely to have an impact on neural connectivity because normal axonal development and synaptic pruning depend on expression of major histocompatibility complex proteins (Huh et al. 2000). The overlap in behavioral symptoms between autism and Fragile X syndrome, a disorder in which synaptic structure is affected, is also consistent with an abnormality of connectivity at the neural level (Belmonte et al. 2004ab). Although several reviews of the genetics of autism are available (Cook 2001, Folstein & Rosen-Sheidley 2001, Lauritsen & Ewald 2001), this is a rapidly developing field.

Future progress in autism research will depend on identifying the ways in which large numbers of genetic biases and environmental factors converge to affect neural structure and dynamics, and the ways in which such abnormalities at the neural level diverge through activity-dependent development to produce an end state in which empathizing abilities are impaired and systemizing abilities are augmented. Such a unified understanding of the psychobiology of autism will offer targets for intervention on many levels.

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