Special Article

Neuroimaging in Disorders of Social and Emotional Functioning: What Is the Question?

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ABSTRACT

Social and emotional processing uses neural systems involving structures ranging from the brain stem to the associational cortex. Neuroimaging research has attempted to identify abnormalities in components of these systems that would underlie the behavioral abnormalities seen in disorders of social and emotional processing, notably autism spectrum disorders, the focus of this review. However, the findings have been variable. The most replicated anatomic finding (a tendency toward large brains) is not modular, and metabolic imaging and functional imaging (although showing substantial atypicality in activation) are not consistent regarding specific anatomic sites. Moreover, autism spectrum disorder demonstrates substantial heterogeneity on multiple levels. Here evidence is marshaled from a review of neuroimaging data to support the claim that abnormalities in social and emotional processing on the autism spectrum are a consequence of systems disruptions in which the behaviors are a final common pathway and the focal findings can be variable, downstream of other pathogenetic mechanisms, and downstream of more pervasive abnormalities. (*J Child Neurol* 2004;19:772–784).

Human beings and many other mammals are social beings; thus, social and emotional mental processes are key to human and, indeed, much mammalian functioning. Some trajectories of evolution have resulted in the emergence of flexibility and nuance in social and emotional capabilities. The neurobiologic substrates of emotional processing are complex and multiple. They involve networks of neural systems ranging from evolutionarily ancient parts of the brain to more complex associational processing that is emergent in larger-brained mammals, particularly higher primates. Because of the interrelationships among these systems, which are rooted in the evolutionarily emergent complexities of brain connectivity,[1,2] it is important to be mindful of the full palette of human social and emotional capabilities in studying these functions and their disorders, as well as of their interplay with other cognitive capacities.

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Social and emotional functions are impaired in a distinctive fashion in disorders on the autism spectrum. Autism is defined purely behaviorally, and a set of three neurobehavioral abnormalities has been found to cluster together, including language impairment, impairment in social reciprocity, and behaviors that are repetitive, ritualistic, or stereotyped.[3] Each of these three features can be described on its own, and they are not all found in equal strength and quality in every individual with autism. Yet although they might seem like modular and dissociable impairments, the clustering of these behavioral features suggests a possible linkage at the level of underlying mechanisms. Indeed, a number of models of underlying cognitive or processing abnormalities have been suggested to underlie these behavioral manifestations, including weak central coherence,[4] impairment of complex processing,[5] and impaired mentalizing or theory of mind.[6]

Various brain, biochemical, immunologic, and genetic abnormalities have been found in individuals on the autism spectrum. Autism can be associated with a range of known disease entities, and it can also be idiopathic.[7] However, at present, it has no reliable biomarkers, making it a syndrome rather than a disease. Moreover, the underlying biology appears to be quite heterogeneous. If there is one constant in studies of biomarkers (eg, neuroanatomy, biochemistry, immunology) for the autism spectrum, it is the presence of variability in measurements. Yet in the setting of such marked variability, individuals whose biologic markers are inconsistent from one to the next have met the full behavioral criteria for autistic disorder, although there is clearly also variability in the way in which subjects can meet these criteria. It has been a

common belief in the field that the variability of measures is a consequence of differences in methodology, whether of subject selection or investigative tools. This notion derives from the assumption that the common behavioral features in these syndromes should rest on a common underlying biology and that were methods and subjects more consistent, it would be easier to identify specific underlying commonalities. However, there is another possibility, which is that some of the variability might be an irreducible intrinsic reflection of the multiple pathways from biology to behavioral phenotype,[8] with the autistic syndrome being not a specific biologic entity but a "final common pathway."

There is another type of variability in these disorders, namely, a difference in behaviors over time in individual subjects. These differences can occur on a day-to-day basis, with "good" and "bad" days or behaviors interspersed among each other. It can also occur over longer intervals, in those cases in which the results of therapeutic interventions lead to more enduring improvements in the level of functioning of affected individuals. These types of variability suggest that there are at least some aspects of the underlying abnormalities that are not strictly "hardwired" but rather are subject to change in various ways. A further type of variability can well be changing the rates of the disorder. A growing number of studies suggest an increase in incidence.[9,10] Although this remains the subject of controversy, if it is even partly true, then the environmental component of the gene-environment interactions underlying the disorder might be changing.[11,12]

The study of brain abnormalities in the autism spectrum has largely aimed to identify brain-behavior correlations. This requires identifying regions of the brain that normally subserve the behaviors that are disordered; however, for the core behavioral features of the spectrum other than language, the relevant normal regional specializations are poorly understood. Even for language, the changes in regional specialization over developmental time, which are highly relevant for developmental disorders, are not clearly known; and regions involved in language domains especially impaired in autism, such as pragmatics, are poorly characterized. Brain-behavior correlation also involves characterizing the neuroanatomic and neurofunctional abnormalities underlying the neurobehavioral impairments. However, this correlational project is challenged by the diversity and inconsistency of the findings among studies and among individuals, some of which are documented below.

In this article, I argue that the data support a shift of interpretive emphasis. Rather than trying to eliminate the variability, I pose the question of just how it can be that such a presumably heterogeneous set of underlying biologic abnormalities can eventuate in the same syndrome of behavioral abnormalities. How can we characterize the cognitive neuroscience of the phenomenon of a final common pathway? I hypothesize that autism is a disorder of systems alteration or disruption and that systems can be impacted in multiple ways and yet yield a similar syndrome of behaviors. From this vantage point, the variability in biomarkers can be transformed from noise into signal,[13] yielding insight into the multiple systems vulnerabilities that can lead to this type of disordered social-emotional functioning. We also need to characterize the limits to the variability of systems impact; that is, under what circumstances can systems disruption lead to a lesser or different syndrome than autism? Formulating the research challenge in these terms can allow a more parsimonious integration not only of variability in biologic findings but also of variability in the gene-environment interactions involved in underlying mechanisms.

ANATOMY OF SOCIAL AND EMOTIONAL PROCESSING

In broad terms, social and emotional behaviors are evolved modes of regulation of individual and group dynamics. At the neuroanatomic level, they involve systems ranging from core somatic regulatory circuitry to circuits modulating action and interaction with objects and beings in the world. They coordinate physiologic adaptations with responses to safety and danger. In more social organisms with more complex intelligences, the environment becomes more functionally differentiated for species with an expanded repertoire of perception and response capabilities.[14] In highly social species, the social environment becomes ever more central to survival, and the evaluation of the intentions, emotions, and thoughts of conspecifics comes to occupy a major place in mental life and in survival. In such organisms, both the social environment and the ability to perceive it strongly affect developmental outcomes. The evolving adaptive and associative intelligence that enables this increasing social complexity cannot be entirely separated from that enabling increasing complexity in mental operations used for material adaptive strategies.

Visceral regulation is an important component of emotional processing and is affected by social experience. Dysfunction in visceral regulation systems can be a component of both dysphoric states and emotional disorders, as well as a consequence of social misfortune. A three-stage model of phylogenetic stages of autonomic nervous system development has been proposed.[15–17] The most primitive stage generates an unmyelinated vegetative vagal system that fosters digestion and that responds to threat by cardiac output reduction and immobilization. A later emerging spinal sympathetic nervous system inhibits the earlier vagal system's influence on the gut and increases the metabolic rate to mobilize for "fight or flight." A third stage, unique to mammals with a myelinated vagal system, is related to regulating cardiac output in relation to engagement and disengagement with the environment. This third system is derived from the branchial or primitive gill arches and thus relates to cranial nerves V, VII, IX, X, and XI. Owing to the functions of these cranial nerves, it is thus related to regulation of components of social engagement that include hearing via middle ear muscles, facial expression via facial musculature, the coordination of breathing with vocalizing via the laryngeal and pharyngeal muscles, and orientation via head-turning muscles. Via rapid vagal regulation of the heart and bronchi, it also modulates rapid social engagement and disengagement. This level of nervous regulation is also associated with fostering early mother-child interactions. Vagal regulation modulates the release of oxytocin and vasopressin, two neuropeptides involved in social bonding and isolation and with responses to safety and fear. Abnormalities in this level of neural systems related to social and emotional behavior have been associated with the autism spectrum, and it is argued that they contribute to the autism. These include brainstem abnormalities,[18–20] abnormalities of oxytocin,[21] and autonomic dysregulation.[22,23]

Moving up the hierarchy, the organism needs to evaluate the emotional content and significance of environmental factors, including social encounters. Many investigations ranging from animal and human lesion studies to functional neuroimaging have implicated the amygdala in this level of social and emotional processing, including demonstrating its role in recognizing facial emotion[24–28] and its assessment of eye gaze direction as a component of assessment of motivation.[29,30] Although the amygdala appears to be involved in evaluating perceptual input for emotional salience, a growing number of studies suggest that the role of the amygdala is more focused on evaluation of fearful stimuli and is more specifically related to states of anxiety.[31,32] Thus, whereas some argue for an amygdala theory of autism,[33,34] others suggest that the role of the amygdala is more modest and not an explanation for the full spectrum of behavioral abnormalities.[35,36]

Participation in social interactions also requires recognition of the specific identity of other individuals.[37] Face recognition is an essential part of this, and the fusiform face area of the ventral cerebral cortex plays a role in this function. Faces appear to be a special class of objects in that they are processed configurally or holistically, as a gestalt, rather than part by part.[38] However, what makes them special is the subject of debate. One model ascribes a domain-specific intrinsic proclivity for face recognition.[39] Counterposed to this is the idea that face recognition is a highly developed form of expert-level configural processing, not intrinsically different from expertise regarding other objects,[40] because configural processing by experts in other domains—for example, by highly experienced bird-watchers—also activates the fusiform face area in functional neuroimaging studies.[41–43] Sheep, on the other hand, use configural processing to recognize other sheep but not familiar human beings.[44] A third model offers a synthesis of aspects of these two models in a developmental framework, proposing that face recognition in the fusiform face area is the result of a developmental process of interactive specialization over time that starts with a preferential orientation to faces in newborns[45] and leads—in interaction with experience and the progressive specialization of brain regions—to the emergence of configural processing of faces.[46] It appears that individuals on the autism spectrum cannot process faces in the same way as typically developed controls,[47–50] although the deficit might not be specific to faces.[51]

Reciprocal social interaction requires an ability to make accurate inferences about the thoughts and mental states of other people. This capacity has been called "theory of mind" or "mentalizing."[52,53] Imaging studies have identified a network of regions associated with this function, including the anterior paracingulate cortex, the superior temporal sulci, and the temporal poles.[54–58] Gallagher and Frith take the modular position, however, that of these three areas, only the paracingulate cortex is uniquely associated with mentalizing, whereas the other two areas activate in association with other functions as well.[59] The anterior cingulate is also involved in multiple functions, including emotion processing.[60]

Processing of emotional and social experience is further modulated in a number of other ways. The cerebellum appears to be involved in affective modulation. It receives information from the associational cortices via the corticopontocerebellar pathway and participates in neural circuits involving the frontal and paralimbic cortices and subcortical structures.[61] Patients with cerebellar lesions can exhibit what has been called the "cerebellar cognitive-affective syndrome."[62] Cerebellar abnormalities were among the first brain abnormalities to be documented in autism.[63,64] The left and right cerebral hemispheres also appear to make different contributions to social and emotional processing, with the right hemisphere seeming to be more configural.[65,66]

Processing of social and emotional stimuli also involves evaluation in the context not only of fresh perceptual information but also of a vast array of past experience. This involves the associational cortex and subcortical relays, such as thalamic nuclei. Certain portions of associational cortex are more highly interconnected with the limbic system. For example, the orbitofrontal and medial prefrontal areas are robustly connected to the amygdala.[67] From an evolutionary point of view, limbic cortical areas have more ancient roots and a less differentiated cortical layering structure, but they preserve a much denser set of interconnections. On the other hand, more recently evolved portions of the cortex, particularly the primary sensory and motor cortex, have a more finely differentiated laminate structure[1]; they are dedicated to the more direct sensory and motor interface with the environment, which they process in a detailed but fractionated and abstracted fashion, and their connections with the rest of the brain are not diverse but rather basically restricted to adjacent regions. The limbic area connections with multiple limbic, polymodal, and premotor cortex regions, as well as with subcortical structure,[2,68] allow these areas to address representations of experience that are less differentiated than those processed by the primary sensory and motor cortex. But these representations contain both multisensory and visceral components and input from many areas at once, allowing a more integrative and regulatory processing to occur.

Social and emotional processing thus does not occur only in isolated nodes but rather requires the interactions of multiple distributed components in relevant neural systems.[69,70] The components of these neural systems are highly interconnected with one another and with other parts of the brain.[71] Disturbances of this processing can be the result of impairments at specific locations in these networks, but they can also be a consequence of altered connectivity between or relationships among the parts. Modeling autism as a systems disturbance requires attending to all such possibilities.

ANATOMIC NEUROIMAGING AND THE ANATOMY OF DISORDERED SOCIAL AND EMOTIONAL BEHAVIOR

Neuroimaging can be used to measure volumes of brain structures. These volumes are affected by cell size and type, cell density, cell organization, extracellular materials, and vasculature.[72] Volume has been thought to be proportional to processing capacity. Early anatomic neuroimaging of autism was markedly influenced by neuropathologic findings of abnormalities in the limbic system and the cerebellum. Owing to both these findings and to early limitations of imaging analysis, a region of interest approach has predominated, with studies documented in Table 1. However, as imaging analysis becomes more sophisticated, it is becoming easier to analyze more regions at once and address the relationships among them. Although abnormalities in multiple components of brain circuitry relevant to social and emotional behavior have

Table 1. Regional Volume Differences From Controls

Smaller	*No Different*	*Larger*
Midline cerebellum lobules V–VII		
Courchesne et al, 1988[74]	Rumsey et al, 1988[84]	Courchesne et al, 1994[83]
Gaffney et al, 1987[80]	Nowell et al, 1990[85]	
Murakami et al, 1989[81]	Elia et al, 2000[86]	
Saitoh et al, 1995[82]	Garber et al, 1992[87]	
	Holtum et al, 1992[88]	
	Kleiman et al, 1992[89]	
	Filipek et al, 1992[91]	
	Piven et al, 1997[92]	
	Piven et al, 1992[90]	
Cerebellar volume		Piven et al, 1997[92]
		Sparks et al, 2002[93]
		Hardan et al, 2001[94]
		Abell et al, 1999[95]
		Courchesne et al, 2001[97]
		Herbert et al, 2003[96]
Hippocampus and/or amygdala		
Aylward et al, 1999[98]	Haznedar et al, 1997[100]	Howard et al, 2000[34]
Herbert et al, 2003[96]	Haznedar et al, 2000[99]	Sparks et al, 2002[93]
	Saitoh et al, 1995[82]	Abell et al, 1999[95]
	Piven et al, 19981[89]	
	Aylward et al, 1999[98]	
White matter		Courchesne et al, 2001[97]
		Carper et al, 2002[121]
		Herbert et al, 2003,[96] 2004[116]
Corpus callosum		
Egaas et al, 1995[128]		
Piven et al, 1997[129]		
Manes et al, 1999[130]		
Hardan et al, 2000[131]		
Herbert et al, 2003[96]		

been documented, the findings are by no means consistent across studies, and many individual findings are not entirely unique to autism. This inconsistency and variability could be due to genuine differences among subjects (which occur even in normal populations,[73] with certain areas of the brain such as tertiary sulci being particularly variable anatomically) or to methodologic problems related to subject selection, imaging acquisition, or imaging analysis. However, there can also be a disconnect between microanatomic abnormalities and macroanatomically detectable volume change. For example, in neuropathologic studies, the limbic system was found to have an increased number of small cells that were densely packed,[64] but the volumetric implications of such a combination of findings are not obvious because the cell size, number, and organization do not all trend in the same direction.

Region of Interest Studies

Cerebellum

Cerebellar area has been measured more often than volume. Determination of area is easier because it minimally requires only the definition of regional boundaries in one sagittal plane. An early report of hypoplasia of cerebellar vermal lobules VI to VII[74] was followed by a substantial number of articles reporting measurements of the midline sagittal area of the cerebellar vermal lobules. These have been reviewed and discussed in detail elsewhere.[75–79] Whereas some of the articles replicated the findings of hypoplasia, others did not. Smaller cerebellar vermal lobules VI to VII were found in several studies,[74,80–82] although some later studies discerned a subgroup with an area increase.[83] However, several other studies found no difference in cerebellar vermal lobules.[84–92]

Volume measurements make more technical demands than area measures; there are fewer reports of cerebellar volume. However, these studies have all described a volume increase. Piven et al and Sparks et al showed a cerebellar increase proportional to increased total brain volume,[92,93] whereas Hardan et al found cerebellar volumes to be both relatively and absolutely larger.[94] A voxel-based morphometry study also found increased gray-matter volume bilaterally in the cerebellum.[95] Herbert et al found that total cerebellar volume was greater in subjects with autism than in controls but not different after adjustment for total brain volume[96]; this finding was in the same brains in which earlier analysis had found no difference in midline vermal lobule VI to VII areas.[91] Cerebellar volume increase can be due to an increase in cerebellar white matter because in the only study in which this was measured, cerebellar white matter was as much as 39% larger in autism than in controls in 2- to 4-year-old children.[97] More research is needed on this phenomenon.

Limbic System

The amygdala was measured to be both absolutely and relatively smaller in one study, in which the hippocampus was found to be only relatively but not absolutely smaller.[96,98] However, it was measured to be larger in several other studies using a variety of methods,[34,93,95] with the last of these studies reporting a subgroup with

proportional enlargement and another subgroup with greater than proportional enlargement. No amygdala volume differences were found by Haznedar et al.[99] The cingulate gyrus, which has been measured less often in neuroanatomic studies, was smaller anteriorly on the right and metabolically less active in two studies by the same group.[100] Small structures are particularly vulnerable to methodologic problems, with both differences among individual raters doing the analyses in the same laboratory and differences in techniques among laboratories potentially contributing to inconsistent results.[99]

Large-Scale Measures

Total Brain Volume

Although region of interest findings have had much variability, the single most replicated finding in autism is a tendency toward unusually large head and brain size: 90% of 2- to 4-year-old children have above-average brain volumes, and up to 37% are frankly macrocephalic.[97] Volume, weight, or size increase has been documented, mainly in younger subjects (but not adults), via a number of classes of data. In this regard, the data from magnetic resonance imaging (MRI) volumetric studies are consistent with measures using other methods. Several studies have reported postmortem measures of brain weight.[63,101,102] In measures of head circumference during life, there has been a substantial upward shift in mean head circumference compared to controls.[103–111] This has also been documented by in vivo MRI volumetric studies.[97,104,112,113] This brain volume increase furthermore appears to occur postnatally, in the first 2 years after birth.[108,114] In older autistic subjects, smaller brain volume has been found to coexist with larger head circumference, suggesting that the brains in these subjects were larger when the subjects were younger[104] and also suggesting possible volume loss over time.

The increased brain volume in autism is an intriguing finding, the basis of which is, at this time, not fully understood. It has generally not had clear cognitive correlates, although one study found a correlation with higher nonverbal IQ.[115] Most of these larger brains appear to be clinically normal and are distinguishable from controls only on the basis of measurements of changes too subtle to be detected by the unaided eye. Normal-looking brains that function poorly do not have a clear precedent in the neurologic literature, and there are thus no obvious models for inferring the underlying mechanisms or the impact on function. Moreover, volume increase is not a modular finding, so its functional implications cannot be inferred from classic notions of brain-behavior correlation. However, volume increase might be implicated in widespread neural systems disruption.

White-Matter Volume Increase and Its Regionalization

Increased brain volume in autism appears to be largely driven by an increase in white matter. In Courchesne et al's study of 2- to 16-year old patients, white-matter enlargement (18% more cerebral and 38% more cerebellar white matter) was found in 2- to 3-year-old children with autism, whereas 12- to 16-year-old adolescents with autism had less white matter than controls.[97] In a comprehensive volumetric profile of high-functioning boys with autism, Herbert et al reported that white matter was 15% larger in boys with autism than in controls and was also the only part of the brain that was also disproportionately larger in subjects with autism.[96] To characterize regional biases in this white-matter volume increase, Herbert et al[116] used a method of topographic white-matter parcellation[117,118] and found that the volume increase is confined to the radiate zone, that is, the subcortical white matter primarily composed of corona radiata and U fibers; the deeper white matter, including the major sagittal tracts, internal capsule, and corpus callosum, showed no volume increase over controls. Myelination proceeds in a gradient from deep to superficial,[119,120] and the areas showing volume enlargement are those that myelinate later. Myelination also proceeds from posterior to anterior, and the frontal lobe white matter showed the greatest enlargement over controls, a finding also reported by Carper et al,[121] with the prefrontal proportion even more strongly affected.[118] The postnatal time course of white-matter volume enlargement suggested by its radiate distribution appears to be consistent with the retrospectively documented postnatal increase in head circumference.[108,114]

Altered Interregional Relationships

Once one entertains a systems disruption model of autism, it becomes of relevance to study not just individual regions of interest but at least as much the relationships among multiple brain structures and neural systems; studies addressing such relationships are documented in Table 2. This is because altered proportionality among components of distributed systems can affect systems properties.[69,122] Although some studies have reported proportional and absolute volumes to adjust for the influence of increased total brain volume, few studies include multiple measures obtained from the same brains, so the relationship among different findings, including ratios and scaling, is often unknown.

Several researchers have found atypical relationships between the frontal lobe and the cerebellum. Carper and Courchesne found an inverse relationship between frontal lobe volume and the area of cerebellar vermal lobules VI to VII.[123] However, although similar reductions in the areas of cerebellar vermal lobules VI to VII were found by Ciesielski et al,[124] they did not appear to be specific to autism (although that might not gainsay their functional relevance).[125] Tsatsanis et al reported a loss of correlation in a group with autism compared with controls between thalamic and total brain volume.[126] In the first whole-brain morphometric profile of autism, Herbert et al reported that the brain volume increase is nonuniform, with the volume differences from controls varying by region.[96] These increases yielded three factors, with white matter alone being disproportionately larger (ie, regarding both absolute and scaled volume), the cerebral cortex and hippocampus-amygdala being absolutely no different but relatively smaller, and the remaining structures being proportionately larger, with greater absolute volumes but scaled volumes no different from those of controls. In this study, white matter made up only about 28 to 30% of cerebral volume but contributed disproportionately to the overall volume increase, accounting for 66% of the volume increase in autism over controls.

Given that the corpus callosum normally varies to the two-thirds power of brain volume,[127] one would expect that in light of brain and white-matter volume increases, the corpus callosum should be larger as well; however, this structure has consistently

Table 2. Altered Interregional Volume Relationships

Carper et al, 2000[123]	Inverse frontal lobe volume to cerebellar area ratios
Tsatsanis et al, 2003[126]	Loss of correlation between thalamic and total brain volume
Herbert et al, 2003[96]	Dissociated nonuniform volume differences in three groups of brain regions compared with controls

been measured to be no different or smaller in subjects with autism than that of controls, albeit with different callosal subdivision emphases among studies. Egaas et al and Piven et al found the corpus callosum to be smaller in autism, mostly posteriorly.[128,129] Manes et al found volume reduction in mentally retarded subjects with autism, mostly in the body of the corpus callosum.[130] Hardan et al found volume reduction in the anterior of the corpus.[131] Herbert et al found no difference in the midsagittal area of the corpus callosum, either as a whole or in any subregion, although there was a trend toward a relative volume decrease in the anterior callosum, which paradoxically connects the parts of the white matter showing the greatest enlargement in the same brains.[118]

The coexistence of expanded white-matter volume with unchanged corpus callosum volume[132] involves an altered ratio between these two linked areas that can change the network properties of brain connectivity and can do so differently for local and intrahemispheric connections than for interhemispheric connections. In addition, larger brain volume is associated with increased functional lateralization.[127] These two dynamics might help account for the widespread alterations in cortical asymmetry reported by Herbert et al in these larger brains, in which there is a substantial increase in a rightwardly asymmetric cortex and a reversal of the right to left cortical asymmetry ratio.[133] Asymmetry is most strongly different from controls in higher-order association cortex, whose development is most experience-dependent.[134,135] These asymmetry alterations are thus likely to be downstream consequences of alterations in volume and connectivity.[133]

Summary of Volumetric Findings

Volume changes in the autism spectrum appear to be composed of a combination of local and diffuse alterations, with more variability in the former. More work is needed on morphometric profiles over time because the differential time trends among regions might give useful information about pathogenesis and functional implications.

METABOLIC STUDIES

Metabolic and functional studies inquire into more dynamic properties of brains. Many metabolic studies of autism have been oriented toward documenting regional metabolic abnormalities in resting subjects, but their results have been variable. Temporal lobe abnormalities have been found by several studies,[136–139] with one such study also identifying abnormal regional cerebral blood flow in the parietal lobe. Delayed frontal lobe maturation has been discerned,[140] and reduced cingulate volume has been associated with a metabolic decrease in the same area in two studies.[99,100] A number of other studies have found abnormalities in multiple regions.[141–143] A few studies have documented altered metabolic relationships among regions. Chiron et al reported reversed left-to-right regional cerebral blood flow indices,[144] whereas Muller et al reported reversed hemispheric dominance to auditory stimulation.[145] A circuit abnormality involving disturbed serotonin synthesis in the dentatothalamocortical pathway was reported by Muller et al,[146] whereas Minshew et al reported a widespread nonlocalized abnormality involving increased membrane degradation products that correlated with neuropsychologic and language deficits.[147] Although each study has advanced a hypothesis to integrate its own findings, none has advanced a hypothesis to integrate the disparate findings among studies.

FUNCTIONAL STUDIES

Among functional neuroimaging studies investigating brain activation associated with social and emotion-processing tasks, one sees the emergence of some common themes, but by no means are the findings entirely consistent among studies. Moreover, there are conceptual and methodologic problems regarding the relationship between the abnormalities identified and their relationship to either underlying causative mechanisms or a broader range of abnormalities with which these findings can coexist. Many functional imaging studies are based on the presumption that the functions under study are modular and that either a failure or alteration of such modules should underlie deficits. However, it is difficult to design a study that not only identifies abnormalities in circuitry but also establishes that this abnormality is primary rather than downstream from circuit problems at other levels. The modular assumption was particularly clearly articulated by Baron-Cohen et al,[148] whose study sought to use functional neuroimaging to confirm the existence of the network of regions discerned by Brothers et al using other methods,[149] which includes the orbitofrontal cortex, superior temporal gyrus, and amygdala and comprises the "social brain." Using a mentalizing task that required judging the emotions of others from their eyes, this network of brain regions activated as predicted for controls but not for subjects with autism, who activated the frontotemporal regions but not the amygdala. Yet although the study was explicitly based on modular assumptions about the dissociability of social from general intelligence, the authors acknowledged that their results still left open the possibility that their subjects with autism had a general deficit in emotional processing rather than a specific deficit in the capacity to infer mental state.

Among the functional neuroimaging studies that have focused on brain activity associated with emotion and face processing, there is a set of studies in which the findings have been primarily related to regions of interest associated with these neurocognitive processes. These investigations were designed on the basis of evidence from the psychologic studies touched on above that face and emotion processing are abnormal in autism. In three studies of face processing in autism, there were deviations from the typical pattern of fusiform face area activation; however, the deviations varied among the studies. In the study by Schultz et al with a task

related to face and object discrimination, face processing showed greater activation in autistic subjects than controls of the inferior temporal gyrus, an area associated in both autistic subjects and controls with the processing of objects.[150] In the study by Critchley et al, the autistic subjects also activated their fusiform gyrus less than controls, but for the task in this study, involving explicit and implicit processing of emotion in faces, they also showed greater activation of the superior temporal and lingual or fusiform gyri than controls.[151] In the study by Pierce et al with a task alternating face with shape perception, control subjects reliably activated the fusiform face area for face processing, whereas the subjects with autism activated areas scattered outside the fusiform face area that varied individually among the subjects.[152] However, Hadjikhani et al reported that subjects with autism do succeed in activating the fusiform face area with face processing and proposed that face processing deficits in autism are due to more complex anomalies in the distributed network of brain areas involved in social perception and cognition.[153]

The variability here thus appears to have several components. First, the tasks differed among the three studies. But, second, as highlighted by the analysis of individual differences in the Pierce et al study,[152] variations among individuals were documented by Pierce et al and could well have been present in the other studies, although such analyses were not reported. Finally, there can be variability regarding attentiveness, although the alteration of circuitry in the light of distractibility is an interesting problem in itself.

Not Anatomic but Systems Anomaly Similarities

Although it might appear that the variability in findings stymies the possibility of identifying the neuroanatomic core of the disordered social and emotional behaviors, the situation, in fact, invites a reframing of results from a different vantage point. The findings do indeed have some common features, but they are at the level of systems design rather than of specific neuroanatomy. Therefore, rather than seek to extract a consensus on the specific anatomic and circuit abnormalities that are associated with specific functional deficits, I instead classify the findings of the studies according to the classes of abnormalities that they have discerned. These abnormalities can be grouped into three classes, as tabulated in Table 3: (1) processing that is more local than global, (2) abnormal either hypo- or hyperconnection among components of neural systems, and (3) marked variability between individuals with autism in sites of activation. I argue that although these classes of findings can be accompanied by substantial inconsistencies at the level of specific anatomic findings, at the level of systems disruption, they are arguably of a piece and consistent.

Local Rather Than Global Processing

The impairment of configural, holistic processing represented by low or a lack of fusiform face area activation in face processing can be understood as a special case of a more widespread problem that has been characterized in such psychologic terms as "weak central coherence"[4] or "impaired complex information processing."[5] Although the precise character of this bias toward local processing is not clear at this time, this tendency has been found in a number of experimental paradigms. Ring et al found evidence that the supernormal domains of ability in autism might, in fact, be enabled by just such local processing.[154] In an embedded figure task, the subjects with autism appeared to use a different processing strategy than controls because although both groups activated areas associated with object and spatial visual processing and object and spatial memory, the subjects with autism failed to activate areas associated with the working memory component of the processing strategy used by controls. In a task that built on prior studies by Schulz,[150] Pierce,[152] and Ring[154] and their colleagues, Hubl et al designed a task to tax both face processing and visual search to discern differential activation beyond the fusiform face area.[155] Although face detection produced the highest fusiform activations in both groups, the signals were lower in the subjects with autism, whereas in the lateral occipital complex, which is more involved in object processing than the fusiform face area, the signal was higher in the group with autism. In a crossmodal (visual and auditory) task involving the enhancement of the emotional salience of facial stimuli by prosodic information, which was selected to amplify the cortical response to facial emotion, Hall et al found that subjects with autism showed diminished right fusiform and inferior frontal activation but greater thalamic, anterior cingulate, and right anterior temporal pole activation, a pattern that suggested less emphasis in these subjects on assembly and evaluation of an integrated emotional experience and greater nonholistic feature analysis.[156] In a bilateral visual spatial attention task, Belmonte and Yurgelun-Todd found that subjects with autism showed higher activations in modality-specific regions, whereas control subjects showed more modality-independent activations.[157]

Altered Connection:
Less or More or Abnormally Distributed

Processing that is local rather than global might, in turn, be either a special case or a consequence of abnormal connections in the brain. An early positron emission tomographic (PET) study by Horwitz et al showed reduced correlations among regions in autistic brains. Ratios of global and regional metabolic rates were calculated from resting PET data of young adult male subjects with autism and control subjects. Although only 4 of 31 regional cerebral metabolic rates for glucose differed between groups, 70% of the 861 possible correlations had lower values in the group with autism; moreover, there were significantly fewer robust correlations in the group with autism than in the control group.[158] However, because autism does not manifest the atrophy present in Alzheimer's disease in which similar reduced correlation is found, the authors attributed these findings to a deficit in attentional mechanisms; they did not entertain other specifically neurobiologic mechanisms that might degrade interregional correlation. A much more recent article has now reported a reduced degree of synchronization of the time series of functional activation between the various participating cortical areas and has placed this finding in the framework of underconnectivity theory.[159]

In Critchley et al's comparison of subjects with autism or Asperger's syndrome and control subjects on a task comparing explicit with implicit emotional judgment, subjects with autism spectrum had less activation of the fusiform gyrus but greater activation of the superior temporal and lingual or fusiform gyri than controls, as well as a lack of amygdalar activation comparable to

Table 3. Functional Imaging: Findings Consistent With Altered Network Properties

Disconnection or loss of variation	
Horwitz et al, 1988[158]	Reduced correlations among regions
Critchley et al, 2000[151]	Apparent failure of top-down regulation
Luna et al, 2002[161]	Dysfunctional integration of circuitry preferentially disabling higher-order cognitive processes
Castelli et al, 2002[162]	Failure of mentalizing network to receive information from upstream areas
Just et al, 2004[159]	Underconnectivity and loss of covariation of activating regions
Local rather than global processing	
Ring et al, 1999[154]	Different processing strategy for embedded figures
Hubl et al, 2003[155]	Greater activation in upstream visual search, less activation in downstream face-specific regions
Hall et al, 2003[156]	Less emphasis on assembly and evaluation of integrated emotional experience; greater nonholistic feature analysis
Belmonte and Yurgelen-Todd, 2003[157]	Higher activation in modality-specific regions; less activation in downstream modality-independent regions
Variability	
Muller et al, 2001[163]	Marked interindividual variability of location among atypical loci of activation in autistic group
Muller et al, 2003[164]	Marked interindividual variability of location among atypical loci of activation in autistic group
Pierce et al, 2001[152]	Marked interindividual variability of location among atypical loci of activation in autistic group
Rumsey et al, 1985[165]	Metabolic ratios highly deviant from mean, with high interindividual variability and scattered throughout the brain
De Volder et al, 1987[166]	Increased interindividual variability in glucose metabolism
Heh et al, 1989[167]	Increased interindividual variability in glucose metabolism

controls for implicit processing.[151] But although the findings appear to fit prominent theories of autism (notably the early mesolimbic formulation of Damasio and Maurer[160]), the authors also noted a broader pattern of activation and raised an intriguing regulatory question regarding whether some of the activations in the autistic group might reflect not primary abnormalities but rather a failure of the top-down regulation that normally modulates these areas. Such a failure could be a problem of degraded connection. Luna et al, in a study of special working memory, found that although regions associated with the performance of visually guided saccades were unimpaired, there was reduced participation of the dorsolateral prefrontal cortex and the posterior cingulate in the more complex task of oculomotor delayed response.[161] These results were interpreted as consistent with a dysfunctional integration of circuitry that would preferentially affect higher-order cognitive processes. Finally, in a study by Castelli et al of the attribution of mental states to animated shapes, the interpretations of the autistic subjects were in almost all cases found to have some element of inaccuracy or inappropriateness that was accompanied by a reduction in areas previously associated with mentalizing but not in the extrastriate component of the network associated with early visual processing.[162] Thus, although the group with autism could detect greater visual complexity, this information did not reach the multimodal brain systems associated with mentalizing in any of the tasks that were presented, raising the question of whether the reduced activation of the mentalizing network (or by implication of the fusiform face area in studies that showed reduction there) was primary or was instead due to these areas failing to receive information from areas earlier in the stream. Belmonte and Yurgelun-Todd interpreted their study results in a framework that responded to this question: they proposed a model of pervasively defective neural and synaptic development yielding hyperaroused primary sensory processing with impaired selectivity of relevant stimuli that overloads higher-order processes and leads to overall inappropriate distribution of sensory activation and excessive attention to detail.[157]

Abnormal Scatter and Variability

In several studies in which activation data were examined on an individual rather than on a group basis, a pattern of variability emerged. Muller et al conducted two successive studies regarding motor movements. In the first, the task was a simple motor movement (visually paced finger movement),[163] whereas in the second, the task involved multimodal processing (visually driven motor sequence learning).[164] In both cases, the Z-scores for the autistic groups were lower than for controls, but this was accounted for by marked individual variability in the loci of activation. However, although the Z-scores for individuals with autism were no different than those for controls, the description of the data is mainly oriented toward localization, leaving it unclear as to whether the activations of individuals with autism are not only centered in aberrant locations but are also larger or more diffuse. Pierce, a member of the same research group, noted a similar variability among individuals with her and her colleagues' observations that face activation occurred in individually varying loci outside of the fusiform gyrus.[152] Another type of variability was appreciated in an early PET study in which Rumsey et al found that multiple subjects with autism (but only one control) showed metabolic ratios that were highly deviant from the mean; these outlier ratios were both variable among patients and scattered throughout the brain.[165] In two other early studies, Devolder et al and Heh et al also noted increased individual variability in regional glucose metabolism among subjects with autism.[166,167]

DISCUSSION

The question was posed in the introduction of how it might be that heterogeneous biologic injuries to neural circuits might lead to a common syndrome of behavioral abnormalities. Taking off from the above categorization of functional neuroimaging abnormalities, the second and third points—local rather than global processing and altered connection—point to circuitry disruptions that do not necessarily have to be tied to specific locations in the circuit. Such

abnormalities could be initiated by focal dysfunction but also by abnormalities that begin with a distributed abnormality to which different regions or neural systems have differential vulnerability.[168] Once an abnormality is present at one level, it can set in motion a sequence of events that amplify the developmental skewing of the system.[132] For example, the behavioral or perceptual abnormality of poor attention to face or emotion processing early in development can impede the experience of attention to face or emotion at a critical period; the lack of intensive experience with faces at this period then joins the self-amplifying feedback loop and alters the developmental course of experience-expectant circuitry.

Increased brain volume and nonuniformly increased white matter can be distributed abnormalities at the tissue and volumetric level implicated in the set of dynamic developmental alterations. Connectivity changes consequent to these volume and tissue abnormalities can alter the function of distributed neural systems with multiple cascading consequences (although functional changes could also be upstream and could lead to use-dependent changes in connectivity or volume). These consequences unfold in the course of early development. Although brain volume increases after birth, it is not known whether the causes of these volume enlargements are prenatal, postnatal, or both. However, insofar as the tissue changes eventuating from the as yet unknown causes emerge in the postnatal period, the postnatal timing of their emergence will shape the impact that they have on circuitry and function.

It appears that the time course of volumetric change interacts with the developmental gradients of white-matter development,[119,120,169,170] so the strongest impact is on the frontal and, in particular, the prefrontal lobes that myelinate last, which are key players in social and emotional processing. If these volume increases reduce the efficiency of connectivity, the impact will reverberate through all of the circuits in which these regions participate.

The case of white-matter enlargement is one of a number of widespread changes that could have heightened impact on specific neural systems, another being altered minicolumns.[171,172] These widespread changes raise the question of the extent to which the specific anatomic locations of abnormal localization might be secondary to disordered systems functioning rather than primary abnormalities in nodes of the circuit. The possibility that node and connection abnormalities might both result from the same underlying disturbances also needs to be considered.

A number of network and systems theories of autism have already been advanced. Lee[173] proposed a model of autism as a circuit system that can result from many different etiologies but focused on the cerebellolimbic circuitry. Cohen proposed a neural network model in which either too many or too few neuronal connections, as documented in the neuropathologic literature, would lead to overemphasis on specific details but an inferior capacity for generalization.[174,175] Brock et al proposed that a reduction in the integration of specialized local neural networks in the brain caused by a deficit in temporal binding would lead to abnormal processing consistent with "weak central coherence."[176] McClelland proposed that hyperspecificity in autism derives from abnormalities in neural nets.[177] Eigsti and Shapiro advanced a systems neuroscience approach highlighting heterogeneous etiologies, diffuse anatomic abnormalities, and neuromodulatory discrepancies rather than gross or localized abnormalities.[178]

If a pervasive abnormality leads to systems-specific consequences,[179-181] its impact is likely to be greatest on functions that are most highly dependent on that which is abnormal. For example, a widespread white-matter abnormality would probably affect connectivity and thus would have a greater impact on functions that are more highly interconnected, as well as on the regions that subserve these functions. At the same time, it is likely to have more subtle but nevertheless detectable impacts on functions that are less dependent on higher-order associational activity. This hypothesis could be tested.

A variety of biologic processes, singly or in combination, could perturb early brain development in ways related to findings noted to lead to the autistic syndrome of disrupted social and emotional behavior. For example, a hypothesis of an increased excitation to inhibition ratio has been proposed[171,182] that could have a series of impacts, including widespread cortical noise that delays or blocks the normal differentiation of brain processing systems, alters memory systems, dysregulates neuromodulatory systems, and interferes with the emergence of systems integration.[182] The finding of altered minicolumn structure[172] could contribute to a decrease in inhibition.[171] An increase in the excitation to inhibition ratio could be the consequence of genetic or environmental influences or both. Such factors can include infectious, immune, or toxic factors, which might alter the milieu of brain development in the autism spectrum and could specifically alter excitation to inhibition ratios.[183,184] White-matter volume increase could be secondary to increased cortical noise because oligodendrocyte activity is modulated by neuronal activity.[185] Oligodendrocytes could also be a primary target of genetic or environmental perturbation[186] because they have some striking vulnerabilities related to their structure, composition, and high energy demand.[187]

The above includes just a small sampling of many mechanisms that could affect brain development in a manner detrimental to social and emotional processing. Which factors will be operative will be variable between individuals. In addition, these factors will show great variability regarding timing and intensity, which will lead to variability of impact. Finally, there is even variability in the expression of abnormal genes owing to factors including the multiple mutations that can occur within a given gene, modulation by a varying combination of other genes, and other epigenetic factors. Thus, it appears that variability in a disorder with heterogeneous etiology is an irreducible given.

There is a further source of variability that can be treatable. Genetic or environmental factors that, early in life, can lead to developmental abnormalities of wiring that become "hardwired" can also—both at the same time and later, after circuitry is more set—affect the biochemical milieu in which brain functioning occurs. A suboptimal chemical milieu, for example, neurotransmitter abnormalities, can also lead to suboptimal connectivity among brain regions, but this milieu might be amenable to treatment in ways that improve functioning without altering brain wiring. That is, there might be an encephalopathy as well as a circuitry component to autism. The chemical milieu might relate to both day-to-day variability in some individuals and to the changes in individuals over time insofar as therapeutic interventions lead to improvements. Imaging and electrophysiologic modalities can thus become tools not only for documenting static brain differences but also for documenting treatment response.

In closing, although neural systems can be identified in normal individuals that subserve social and emotional functioning, disorders of these capacities can result from diffuse and distributed abnormalities and focal changes in these systems. Failure to activate a region might be due to histopathologic abnormality in that region, but it might also be due to systems abnormalities. This implies a partial dissociation between mechanisms of pathogenesis and histogenetic injury on the one hand and the cognitive neuroscience of social-emotional functioning and its disorders on the other.[188] Investigations of the cognitive neuroscience of developmental social and emotional disorders need to encompass both variability and systems disturbances in their hypotheses about the nature of the disorders. Investigations of pathogenesis might lead to understanding of mechanisms and to treatments, as well as to new means of understanding the variability in these disorders.

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References

1. Sanides F: Functional architecture of motor and sensory cortices in primates in the light of a new concept of neocortex evolution, in Noback CR, Montagna W (eds): *The Primate Brain: Advances in Primatology.* New York, Meredith Corp, 1970, 137–208.
2. Barbas H: Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. *Neurosci Biobehav Rev* 1995;19:499–510.
3. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC, American Psychiatric Association, 1994.
4. Frith U, Happe F: Autism: Beyond the 'theory of mind.' *Cognition* 1994;50:115–132.
5. Minshew J, Goldstein G, Siegel D: Neuropsychologic functioning in autism: Profile of a complex informational processing disorder. *J Int Neuropsychol Soc* 1997;3:303–316.
6. Frith U: Mind blindness and the brain in autism. Neuron 2001;32:969–979.
7. Gillberg C, Coleman M: *The Biology of the Autistic Syndromes (Clinics in Developmental Medicine)*. Cambridge, UK, Cambridge University Press, 2000.
8. Morton J, Frith U: Causal modelling: A structural approach to developmental psychopathology, in Cicchetti D, Cohen DJ (eds): *Manual of Developmental Psychopathology.* New York, John Wiley, 1995, 357–390.
9. Fombonne E: Epidemiological surveys of autism and other pervasive developmental disorders: An update. *J Autism Dev Disord* 2003;33:365–382.
10. Blaxill M: What's going on? The question of time trends in autism. *Public Health Rep* 2004; in press.
11. Stein J, Schettler T, Wallinga D, Valenti M: In harm's way: Toxic threats to child development. *J Dev Behav Pediatr* 2002;23(1 Suppl):S13–S22.
12. Allred M, Wilbur S: Hazardous substance exposures and autism, in DeRosa C, Holler J, Mehlman M (eds): *Advances in Modern Toxicology.* Princeton, NJ, International Toxicology Books, Inc, 2002.
13. Smith LB, Thelen E: Development as a dynamic system. *Trends Cogn Sci* 2003;7:343–348.
14. Maier NRF, Schneirla TC: *Principles of Animal Psychology.* New York, Dover Publications, 1964.
15. Porges SW: Emotion: An evolutionary by-product of the neural regulation of the autonomic nervous system. *Ann N Y Acad Sci* 1997;807:62–77.
16. Porges SW: The polyvagal theory: Phylogenetic contributions to social behavior. *Physiol Behav* 2003;79:503–513.
17. Porges S: The vagus: A mediator of behavioral and visceral features associated with autism, in Bauman M, Kemper T (eds): *The Neurobiology of Autism.* 2004, Baltimore, John Hopkins University Press, in press..
18. Rodier PM, Ingram JL, Tisdale B, et al: Embryological origins for autism: Developmental anomalies of the cranial nerve motor nuclei. *J Comp Neurol* 1996;370:247–261.
19. Rodier PM: Converging evidence for brain stem injury in autism. *Dev Psychopathol* 2002;14:537–557.
20. Rosenhall U, Nordin V, Brantberg K, Gillberg C: Autism and auditory brain stem responses. *Ear Hear* 2003;24:206–214.
21. Insel TR, O'Brien DJ, Leckman JF: Oxytocin, vasopressin, and autism: Is there a connection? *Biol Psychiatry* 1999;45:145–157.
22. Toichi M, Kamio Y: Paradoxical autonomic response to mental tasks in autism. *J Autism Dev Disord* 2003;33:417–426.
23. Hirstein W, Iversen P, Ramachandran VS: Autonomic responses of autistic children to people and objects. *Proc R Soc Lond B Biol Sci* 2001; 268:1883–1888.
24. Breiter HC, Etcoff NL, Whalen PJ, et al: Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* 1996;17:875–887.
25. Morris JS, Frith CD, Perrett DI, et al: A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature* 1996;383:812–815.
26. Whalen PJ, Rauch SL, Etcoff NL, et al: Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci* 1998;18:411–418.
27. Whalen PJ, Shin LM, McInerney SC, et al: A functional MRI study of human amygdala responses to facial expressions of fear versus anger. *Emotion* 2001;1:70–83.
28. Canli T, Sivers H, Whitfield SL, et al: Amygdala response to happy faces as a function of extraversion. *Science* 2002;296:2191.
29. Hooker CI, Paller KA, Gitelman DR, et al: Brain networks for analyzing eye gaze. *Brain Res Cogn Brain Res* 2003;17:406–418.
30. Kawashima R, Sugiura M, Kato T, et al: The human amygdala plays an important role in gaze monitoring. A PET study. *Brain* 1999;122(Pt 4):779–783.
31. Adolphs R: Is the human amygdala specialized for processing social information? *Ann N Y Acad Sci* 2003:985;326–340.
32. Davidson RJ: Anxiety and affective style: Role of prefrontal cortex and amygdala. *Biol Psychiatry* 2002;51:68–80.
33. Baron-Cohen S, Ring HA, Bullmore ET, et al: The amygdala theory of autism. *Neurosci Biobehav Rev* 2000;24:355–364.
34. Howard MA, Cowell PE, Boucher J, et al: Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. *Neuroreport* 2000;11:2931–2935.
35. Amaral DG, Bauman MD, Schumann CM: The amygdala and autism: Implications from non-human primate studies. *Genes Brain Behav* 2003;2:295–302.
36. Amaral DG, Corbett BA: The amygdala, autism and anxiety. *Novartis Found Symp* 2003;251:177–187; discussion 187–197, 281–297.
37. Haxby JV, Hoffman EA, Gobbini MI: Human neural systems for face recognition and social communication. *Biol Psychiatry* 2002;51:59–67.
38. Mondloch CJ, Le Grand R, Maurer D: Configural face processing develops more slowly than featural face processing. *Perception* 2002;31:553–566.
39. Kanwisher N: Domain specificity in face perception. *Nat Neurosci* 2000;3:759–763.
40. Elgar K, Campbell R: Annotation: The cognitive neuroscience of face recognition: Implications for developmental disorders. *J Child Psychol Psychiatry* 2001;42:705–717.
41. Tarr MJ, Gauthier I: FFA: A flexible fusiform area for subordinate-level visual processing automatized by expertise. *Nat Neurosci* 2000;3:764–769.
42. Grelotti DJ, Gauthier I, Schultz RT: Social interest and the development of cortical face specialization: What autism teaches us about face processing. *Dev Psychobiol* 2002;40:213–225.
43. Chao LL, Martin A, Haxby JV: Are face-responsive regions selective only for faces? *Neuroreport* 1999;10:2945–2950.

44. Pierce JW, Leigh AE, daCosta AP, Kendrick KM: Human face recognition in sheep: Lack of configurational coding and right hemisphere advantage. *Behav Process* 2001;55:13–26.
45. Johnson MH, Dziurawiec S, Ellis H, Morton J: Newborns' preferential tracking of face-like stimuli and its subsequent decline. *Cognition* 1991;40:1–19.
46. de Haan M, Humphreys K, Johnson MH: Developing a brain specialized for face perception: A converging methods approach. *Dev Psychobiol* 2002;40:200–212.
47. Hauck M, Fein D, Maltby N, et al: Memory for faces in children with autism. *Child Neuropsychol* 1998;4:187–198.
48. Boucher J, Lewis V: Unfamiliar face recognition in relatively able autistic children. *J Child Psychol Psychiatry* 1992;33:843–859.
49. Haxby JV, Ungerleider LG, Clark VP, et al: The effect of face inversion on activity in human neural systems for face and object perception. *Neuron* 1999;22:189–199.
50. Joseph RM, Tanaka J: Holistic and part-based face recognition in children with autism. *J Child Psychol Psychiatry* 2003;44:529–542.
51. Davies S, Bishop D, Manstead AS, Tantam D: Face perception in children with autism and Asperger's syndrome. *J Child Psychol Psychiatry* 1994;35:1033–1057.
52. Premack D, Woodruff G: Does the chimpanzee have a theory of mind? *Behav Brain Sci* 1978;4:515–526.
53. Happe F: Theory of mind and the self. *Ann N Y Acad Sci* 2003;1001: 134–144.
54. Castelli F, Happe F, Frith U, Frith C: Movement and mind: A functional imaging study of perception and interpretation of complex intentional movement patterns. *Neuroimage* 2000;12:314–325.
55. Gallagher HL, Happe F, Brunswick N, et al: Reading the mind in cartoons and stories: An fMRI study of 'theory of mind' in verbal and nonverbal tasks. *Neuropsychologia* 2000;38:11–21.
56. Goel V, Grafman J, Sadato N, Hallett M: Modeling other minds. *Neuroreport* 1995;6:1741–1746.
57. Brunet E, Sarfati Y, Hardy-Bayle MC, Decety J: A PET investigation of the attribution of intentions with a nonverbal task. *Neuroimage* 2000;11:157–166.
58. Vogeley K, Bussfeld P, Newen A, et al: Mind reading: Neural mechanisms of theory of mind and self-perspective. *Neuroimage* 2001;14:170–181.
59. Gallagher HL, Frith CD: Functional imaging of 'theory of mind.' *Trends Cogn Sci* 2003;7:77–83.
60. Bush G, Luu P, Posner MI: Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 2000;4:215–222.
61. Schmahmann JD: The cerebellum in autism: Clinical and anatomic perspectives, in Bauman ML, Kemper TL (eds): *The Neurobiology of Autism.* Baltimore, MD, Johns Hopkins University Press, 1994, 195–226.
62. Schmahmann JD, Sherman JC: The cerebellar cognitive affective syndrome. *Brain* 1998;121(Pt 4):561–579.
63. Bauman ML, Kemper TL: Histoanatomic observations of the brain in early infantile autism. *Neurology* 1985;35:866–874.
64. Bauman ML, Kemper TL: Neuroanatomic observations of the brain in autism, in Bauman ML, Kemper TL (eds): *The Neurobiology of Autism.* Baltimore, MD, Johns Hopkins University Press, 1994, 119–145.
65. Ross ED, Thompson RD, Yenkosky J: Lateralization of affective prosody in brain and the callosal integration of hemispheric language functions. *Brain Lang* 1997;56:27–54.
66. Ivry R, Robertson L: A theory of hemispheric asymmetries in perception, in Ivry R, Robertson L (eds): *The Two Sides of Perception.* Cambridge, MA, MIT Press, 1997, 33–71.
67. Ghashghaei HT, Barbas H: Pathways for emotion: Interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience* 2002;115:1261–1279.
68. Tucker DM: Developing emotions and cortical networks, in Gunnar MR, Nelson CA (eds): *Developmental Behavioral Neuroscience.* Hillsdale, NJ, Lawrence Erlbaum Associates, 1992, 75–128.
69. Mesulam MM: Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol* 1990;28:597–613.
70. Mesulam MM: *Principles of Behavioral Neurology.* New York, Oxford University Press, 2000.
71. Mesulam MM: From sensation to cognition. *Brain* 1998;121(Pt 6):1013–1052.
72. Caviness VS Jr, Lange NT, Makris N, et al: MRI-based brain volumetrics: Emergence of a developmental brain science. *Brain Dev* 1999;21:289–295.
73. Lange N, Giedd JN, Castellanos FX, et al: Variability of human brain structure size: Ages 4-20 years. *Psychol Res Neuroimaging* 1997;74:1–12.
74. Courchesne E, Yeung-Courchesne R, Pres GA, et al: Hypoplasia of cerebellar vermal lobules VI and VII in autism. *N Engl J Med* 1988;318:1349–1354.
75. Filipek PA: Quantitative magnetic resonance imaging in autism: The cerebellar vermis. *Curr Opin Neurol* 1995;8:134–138.
76. Piven J, Arndt S: The cerebellum and autism. *Neurology* 1995;45: 398–399.
77. Courchesne E, Townsend J, Saitoh O: Reply from the authors to Piven & Arndt. *Neurology* 1995;45:399–402.
78. Courchesne E: An MRI study of autism: The cerebellum revisited. *Neurology* 1999;52:1106
79. Piven J, Saliba K, Bailey J, Arndt S: An MRI study of autism: The cerebellum revisited—Reply. *Neurology* 1999;52:1106–1107.
80. Gaffney GR, Tsai LY, Kuperman S, Minchin S: Cerebellar structure in autism. *Am J Dis Child* 1987;141:1330–1332.
81. Murakami JW, Courchesne E, Press GA, et al: Reduced cerebellar hemisphere size and its relationship to vermal hypoplasia in autism. *Arch Neurol* 1989;46:689–694.
82. Saitoh O, Courchesne E, Egaas B, et al: Cross-sectional area of the posterior hippocampus in autistic patients with cerebellar and corpus callosum abnormalities. *Neurology* 1995;45:317–324.
83. Courchesne E, Saitoh O, Yeung-Courchesne R, et al: Abnormality of cerebellar vermian lobules VI and VII in patients with infantile autism: Identification of hypoplastic and hyperplastic subgroups with MR imaging. *AJR Am J Roentgenol* 1994;162:123–130.
84. Rumsey JM, Hamburger SD: Neuropsychological findings in high-functioning men with infantile autism residual state. *J Clin Exp Neuropsychol* 1988;10:201–221.
85. Nowell MA, Hackney DB, Muraki AS, Coleman M: Varied MR appearance of autism: Fifty-three pediatric patients having the full autistic syndrome. *Magn Reson Imaging* 1990;8:811–816.
86. Elia M, Ferri R, Musumeci SA, et al: Clinical correlates of brain morphometric features of subjects with low-functioning autistic disorder. *J Child Neurol* 2000;15:504–508.
87. Garber HI, Ritvo ER: Magnetic resonance imaging of the posterior fossa in autistic adults. *Am J Psychiatry* 1992;149:245–247.
88. Holttum JR, Minshew NJ, Sanders RS, Phillips NE: Magnetic resonance imaging of the posterior fossa in autism. *Biol Psychiatry* 1992; 32:1091–1101.
89. Kleiman MD, Neff S, Rosman NP: The brain in infantile autism: Are posterior fossa structures abnormal? *Neurology* 1992;42:753–760.
90. Piven J, Nehme E, Simon J, et al: Magnetic resonance imaging in autism: Measurement of the cerebellum, pons, and fourth ventricle. *Biol Psychiatry* 1992;31:491–504.
91. Filipek P, Richelme C, Kennedy D, et al: Morphometric analysis of the brain in developmental language disorders and autism, abstract. *Ann Neurol* 1992;32:475.
92. Piven J, Saliba K, Bailey J, Arndt S: An MRI study of autism: The cerebellum revisited. *Neurology* 1997;49:546–551.
93. Sparks BF, Friedman SD, Shaw DW, et al: Brain structural abnormalities in young children with autism spectrum disorder. *Neurology* 2002;59:184–192.
94. Hardan AY, Minshew NJ, Harenski K, Keshavan MS: Posterior fossa magnetic resonance imaging in autism. *J Am Acad Child Adolesc Psychiatry* 2001;40:666–672.
95. Abell F, Krams M, Ashburner J, et al: The neuroanatomy of autism: A voxel-based whole brain analysis of structural scans. *Neuroreport* 1999;10:1647–1651.

96. Herbert MR, Ziegler DA, Deutsch CK, et al: Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. *Brain* 2003;126:1182–1192.
97. Courchesne E, Karns CM, Davis HR, et al: Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. *Neurology* 2001;57:245–254.
98. Aylward EH, Minshew NJ, Goldstein G, et al: MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. *Neurology* 1999;53:2145–2150.
99. Haznedar MM, Buchsbaum MS, Wei TC, et al: Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. *Am J Psychiatry* 2000;157:1994–2001.
100. Haznedar MM, Buchsbaum MS, Metzger M, et al: Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. *Am J Psychiatry* 1997;154:1047–1050.
101. Bailey A, Luthert P, Dean A, et al: A clinicopathological study of autism. *Brain* 1998;121:889–905.
102. Kemper TL, Bauman M: Neuropathology of infantile autism. *J Neuropathol Exp Neurol* 1998;57:645–652.
103. Bailey A, Luthert P, Bolton P, et al: Autism and megalencephaly. *Lancet* 1993;34:1225–1226.
104. Aylward EH, Minshew NJ, Field K, et al: Effects of age on brain volume and head circumference in autism. *Neurology* 2002;59:175–183.
105. Fidler DJ, Bailey JN, Smalley SL: Macrocephaly in autism and other pervasive developmental disorders. *Dev Med Child Neurol* 2000;42: 737–740.
106. Miles JH, Hadden LL, Takahashi TN, Hillman RE: Head circumference is an independent clinical finding associated with autism. *Am J Med Genet* 2000;95:339–350.
107. Rapin I: *Preschool Children With Inadequate Communication: Developmental Language Disorder, Autism, Low IQ*. London, Mac Keith Press, 1996.
108. Lainhart JE, Piven J, Wzorek M, et al: Macrocephaly in children and adults with autism. *J Am Acad Child Adolesc Psychiatry* 1997;36: 282–290.
109. Davidovitch M, Patterson B, Gartside P: Head circumference measurements in children with autism. *J Child Neurol* 1996;11:389–393.
110. Woodhouse W, Bailey A, Rutter M, et al: Head circumference in autism and other pervasive developmental disorders. *J Child Psychol Psychiatry* 1996;37:665–671.
111. Fombonne E: The epidemiology of autism: A review. *Psychol Med* 1999;29:769–786.
112. Piven J, Arndt S, Bailey J, et al: An MRI study of brain size in autism. *Am J Psychiatry* 1995;152:1145–1149.
113. Piven J, Arndt S, Bailey J, Andreasen N: Regional brain enlargement in autism: A magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry* 1996;35:530–536.
114. Courchesne E, Carper R, Akshoomoff N: Evidence of brain overgrowth in the first year of life in autism. *JAMA* 2003;290:337–344.
115. Deutsch CK, Joseph RM: Brief report: Cognitive correlates of enlarged head circumference in children with autism. *J Autism Dev Disord* 2003;33:209–215.
116. Herbert MR, Ziegler DA, Makris N, et al: Localization of white matter volume increase in autism and developmental language disorder. *Ann Neurol* 2004;55:530–540.
117. Meyer J, Makris N, Bates J, et al: Parcellation of the human cerebral white matter: An MRI-based computational system. Part I: Technical foundations. *Neuroimage* 1999;9:1–17.
118. Makris N, Meyer JW, Bates JF, et al: MRI-based topographic parcellation of human cerebral white matter and nuclei II. Rationale and applications with systematics of cerebral connectivity. *Neuroimage* 1999;9:18–45.
119. Yakovlev PI , Lecours A-R: The myelogenetic cycles of regional maturation of the brain, in Minkowski A (ed): *Regional Development of the Brain in Early Life.* Oxford, UK, Blackwell Scientific Publications, 1967, 3–70.
120. Kinney HC, Brody BA, Kloman AS, Gilles FH: Sequence of central nervous system myelination in human infancy. II: Patterns of myelination in autopsied infants. *J Neuropathol Exp Neurol* 1988;47:217–234.
121. Carper RA, Moses P, Tigue ZD, Courchesne E: Cerebral lobes in autism: Early hyperplasia and abnormal age effects. *Neuroimage* 2002;16:1038–1051.
122. Andrews TJ, Halpern SD, Purves D: Correlated size variations in human visual cortex, lateral geniculate nucleus, and optic tract. *J Neurosci* 1997;17:2859–2868.
123. Carper RA, Courchesne E: Inverse correlation between frontal lobe and cerebellum sizes in children with autism. *Brain* 2000;123(Pt 4):836–844.
124. Ciesielski KT, Harris RJ, Hart BL, Pabst HF: Cerebellar hypoplasia and frontal lobe cognitive deficits in disorders of early childhood. *Neuropsychologia* 1997;35:643–655.
125. Ciesielski KT, Knight JE: Cerebellar abnormality in autism: A nonspecific effect of early brain damage? *Acta Neurobiol Exp (Warsz)* 1994;54:151–154.
126. Tsatsanis KD, Rourke BP, Klin A, et al: Reduced thalamic volume in high-functioning individuals with autism. *Biol Psychiatry* 2003;53:121–129.
127. Jancke L, Staiger JF, Schlaug G, et al: The relationship between corpus callosum size and forebrain volume. *Cereb Cortex* 1997;7:48–56.
128. Egaas B, Courchesne E, Saitoh O: Reduced size of corpus callosum in autism. *Arch Neurol* 1995;52:794–801.
129. Piven J, Bailey J, Ranson BJ, Arndt S: An MRI study of the corpus callosum in autism. Am J Psychiatry 1997;154:1051–1056.
130. Manes F, Piven J, Vrancic D, et al: An MRI study of the corpus callosum and cerebellum in mentally retarded autistic individuals. *J Neuropsychiatry Clin Neurosci* 1999;11:470–474.
131. Hardan AY, Minshew NJ, Keshavan MS: Corpus callosum size in autism. Neurology 2000;55:1033–1036.
132. Belmonte MK, Cook EH, Anderson GM, et al: Autism as a disorder of neural information processing: Directions for research and targets for therapy (1). *Mol Psychiatry* 2004;9:646-663.
133. Herbert MR, Ziegler DA, Deutsch CK, et al: Brain asymmetries in autism and developmental language disorder: A nested whole-brain analysis. 2004; in press.
134. Kingsbury MA, Finlay BL: The cortex in multidimensional space: Where do cortical areas come from? *Dev Sci* 2001;4:125–156.
135. Krubitzer L, Kahn DM: Nature versus nurture revisited: An old idea with a new twist. *Prog Neurobiol* 2003;70:33–52.
136. Mountz JM, Tolbert LC, Lill DW, et al: Functional deficits in autistic disorder: Characterization by technetium-99m-HMPAO and SPECT. *J Nucl Med* 1995;36:1156–1162.
137. Chugani HT, Da Silva E, Chugani DC: Infantile spasms: III. Prognostic implications of bitemporal hypometabolism on positron emission tomography. *Ann Neurol* 1996;39:643–649.
138. Zilbovicius M, Boddaert N, Belin P, et al: Temporal lobe dysfunction in childhood autism: A PET study. Positron emission tomography. *Am J Psychiatry* 2000;157:1988–1993.
139. Boddaert N, Zilbovicius M: Functional neuroimaging and childhood autism. *Pediatr Radiol* 2002;32:1–7.
140. Zilbovicius M, Garreau B, Samson Y: Delayed maturation of the frontal cortex in childhood autism. *Am J Psychiatry* 1995;158:248–252.
141. Ryu YH, Lee JD, Yoon PH, et al: Perfusion impairments in infantile autism on technetium-99m ethyl cysteinate dimer brain single-photon emission tomography: Comparison with findings on magnetic resonance imaging. *Eur J Nucl Med* 1999;26:253–259.
142. Ohnishi T, Matsuda H, Hashimoto T, et al: Abnormal regional cerebral blood flow in childhood autism. *Brain* 2000;123(Pt 9):1838–1844.
143. Wilcox J, Tsuang MT, Ledger E, et al: Brain perfusion in autism varies with age. *Neuropsychobiology* 2002;46:13–16.
144. Chiron C, Leboyer M, Leon F, et al: SPECT of the brain in childhood autism: Evidence for a lack of normal hemispheric asymmetry. *Dev Med Child Neurol* 1995;37:849–860.
145. Muller RA, Behen ME, Rothermel RD, et al: Brain mapping of language and auditory perception in high-functioning autistic adults: A PET study. *J Autism Dev Disord* 1999;29:19–31.
146. Muller RA, Chugani DC, Behen ME, et al: Impairment of dentato-thalamo-cortical pathway in autistic men: Language activation data from positron emission tomography. *Neurosci Lett* 1998;245:1–4.

147. Minshew NJ, Goldstein G, Dombrowski SM, et al: A preliminary 31P MRS study of autism: Evidence for undersynthesis and increased degradation of brain membranes. *Biol Psychiatry* 1993;33:762-773

148. Baron-Cohen S, Ring HA, Wheelwright S, et al: Social intelligence in the normal and autistic brain: An fMRI study. *Eur J Neurosci* 1999;11:1891–1898.

149. Brothers L, Ring B, Kling A: Response of neurons in the macaque amygdala to complex social stimuli. *Behav Brain Res* 1990;41:199–213.

150. Schultz RT, Gauthier I, Klin A, et al: Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. *Arch Gen Psychiatry* 2000;57:331–340.

151. Critchley HD, Daly EM, Bullmore ET, et al: The functional neuroanatomy of social behaviour: Changes in cerebral blood flow when people with autistic disorder process facial expressions. *Brain* 2000;123(Pt 11):2203–2212.

152. Pierce K, Muller RA, Ambrose J, et al: Face processing occurs outside the fusiform 'face area' in autism: Evidence from functional MRI. *Brain* 2001;124:2059–2073.

153. Hadjikhani H, Joseph RM, Snyder J, et al: Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. 2004; *Neuroimage* 2004; 22:1141-1150.

154. Ring HA, Baron-Cohen S, Wheelwright S, et al: Cerebral correlates of preserved cognitive skills in autism: A functional MRI study of embedded figures task performance. *Brain* 1999;122(Pt 7):1305–1315.

155. Hubl D, Bolte S, Feineis-Matthews S, et al: Functional imbalance of visual pathways indicates alternative face processing strategies in autism. *Neurology* 2003;61:1232–1237.

156. Hall GB, Szechtman H, Nahmias C: Enhanced salience and emotion recognition in autism: A PET study. *Am J Psychiatry* 2003;160: 1439–1441.

157. Belmonte MK, Yurgelun-Todd DA: Functional anatomy of impaired selective attention and compensatory processing in autism. *Brain Res Cogn Brain Res* 2003;17:651–664.

158. Horwitz B, Rumsey JM, Grady CL, Rapoport SI: The cerebral metabolic landscape in autism. Intercorrelations of regional glucose utilization. *Arch Neurol* 1988;45:749–755.

159. Just MA, Cherkassky VL, Keller TA, Minshew NJ: Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain* 2004;127(Pt 8):1811–1821.

160. Damasio A, Maurer R: A neurological model for childhood autism. *Arch Neurol* 1978;35:777–863.

161. Luna B, Minshew NJ, Garver KE, et al: Neocortical system abnormalities in autism: An fMRI study of spatial working memory. *Neurology* 2002;59:834–840.

162. Castelli F, Frith C, Happe F, Frith U: Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain* 2002;125:1839–1849.

163. Muller RA, Pierce K, Ambrose JB, et al: Atypical patterns of cerebral motor activation in autism: A functional magnetic resonance study. *Biol Psychiatry* 2001;49:665–676.

164. Muller RA, Kleinhans N, Kemmotsu N, et al: Abnormal variability and distribution of functional maps in autism: An fMRI study of visuomotor learning. *Am J Psychiatry* 2003;160:1847–1862.

165. Rumsey J, Duara R, Grady C, et al: Brain metabolism in autism: Resting cerebral glucose utilization rates as measured with positron emission tomography. *Arch Gen Psychiatry* 1985;42:448–455.

166. De Volder A, Bol A, Michel C, et al: Brain glucose metabolism in children with the autistic syndrome: Positron tomography analysis. *Brain Dev* 1987;9:581–587.

167. Heh CW, Smith R, Wu J, et al: Positron emission tomography of the cerebellum in autism. *Am J Psychiatry* 1989;146:242–245.

168. Caviness VS: Research strategies in autism: A story with two sides. *Curr Opin Neurol* 2001;14:141–143.

169. Barkovich AJ, Lyon G, Evrard P: Formation, maturation, and disorders of white matter. *AJNR Am J Neuroradiol* 1992;13:447–461.

170. Sampaio R, Truwit C: Myelination in the developing human brain, in Nelson C, Luciana M (eds): *Handbook of Developmental Cognitive Neuroscience.* Cambridge, MA, MIT Press, 2001, 35–44.

171. Casanova MF, Buxhoeveden D, Gomez J: Disruption in the inhibitory architecture of the cell minicolumn: Implications for autism. *Neuroscientist* 2003;9:496–507.

172. Casanova MF, Buxhoeveden DP, Switala AE, Roy E: Minicolumnar pathology in autism. *Neurology* 2002;58:428–432.

173. Lee DA, Lopez-Alberola R, Bhattacharjee M: Childhood autism: a circuit syndrome? *Neurologist* 2003;9:99–109.

174. Cohen IL: An artificial neural network analogue of learning in autism. *Biol Psychiatry* 1994;36:5–20.

175. Cohen IL: A neural network model of autism: Implications for theory and treatment, in Mareschal D, Sirois S, Westermann G, Johnson MH (eds): *Neuroconstructivism, Volume 2: Perspectives and Prospects.* Oxford, UK, Oxford University Press, 2004, in press.

176. Brock J, Brown CC, Boucher J, Rippon G: The temporal binding deficit hypothesis of autism. *Dev Psychopathol* 2002;14:209–224.

177. McClelland JL: The basis of hyperspecificity in autism: A preliminary suggestion based on properties of neural nets. *J Autism Dev Disord* 2000;30:497–502.

178. Eigsti IM, Shapiro T: A systems neuroscience approach to autism: Biological, cognitive, and clinical perspectives. *Ment Retard Dev Disabil Res Rev* 2003;9:205–215.

179. Karmiloff-Smith A: Development itself is the key to understanding developmental disorders. *Trends Cogn Sci* 1998;2:389–398.

180. Paterson SJ, Brown JH, Gsodl MK, et al: Cognitive modularity and genetic disorders. *Science* 1999;286:2355–2358.

181. Johnson MH, Halit H, Grice SJ, Karmiloff-Smith A: Neuroimaging of typical and atypical development: A perspective from multiple levels of analysis. *Dev Psychopathol* 2002;14:521–536.

182. Rubenstein JL, Merzenich MM: Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav* 2003;2:255–267.

183. Hornig M, Lipkin WI: Infectious and immune factors in the pathogenesis of neurodevelopmental disorders: Epidemiology, hypotheses, and animal models. *Ment Retard Dev Disabil Res Rev* 2001;7:200–210.

184. Dalton P, Deacon R, Blamire A, et al: Maternal neuronal antibodies associated with autism and a language disorder. *Ann Neurol* 2003; 53:533–537.

185. Barres BA, Raff MC: Axonal control of oligodendrocyte development. *J Cell Biol* 1999;147:1123–1128.

186. Tiffany-Castiglioni E, Guerri C, Aschner M, et al: Roles of glia in developmental neurotoxicity: Session VI summary and research needs. *Neurotoxicology* 2001;22:567–573.

187. Bartzokis G: Age-related myelin breakdown: A developmental model of cognitive decline and Alzheimer's disease. *Neurobiol Aging* 2004;25:5–18.

188. Herbert, M. Loose coupling of pathogenesis-brain-behavior correlations. Submitted.

189. Piven J; Bailey, J; Ranson BJ., and Arndt S. No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. *J Autism Dev Disord.* 1998;28:105-10.