The New Neurobiology of Autism

Cortex, Connectivity, and Neuronal Organization

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This review covers a fraction of the new research developments in autism but establishes the basic elements of the new neurobiologic understanding of autism. Autism is a polygenetic developmental neurobiologic disorder with multiorgan system involvement, though it predominantly involves central nervous system dysfunction. The evidence supports autism as a disorder of the association cortex, both its neurons and their projections. In particular, it is a disorder of connectivity, which appears, from current evidence, to primarily involve intrahemispheric connectivity. The focus of connectivity studies thus far has been on white matter, but alterations in functional magnetic resonance imaging activation suggest that intracortical connectivity is also likely to be disturbed. Furthermore, the disorder has a broad impact on cognitive and neurologic functioning. Deficits in high-functioning individuals occur in processing that places high demands on integration of information and coordination of multiple neural systems. Intact or enhanced abilities share a dependence on low information-processing demands and local neural connections. This multidomain model with shared characteristics predicts an underlying pathophysiologic mechanism that impacts the brain broadly, according to a common neurobiologic principle. The multiorgan system involvement and diversity of central nervous system findings suggest an epigenetic mechanism.

In the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition), autism is the prototype for the category called pervasive developmental disorders. Of the pervasive developmental disorders, autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified are informally referred to as the autism spectrum disorders (ASDs), which may affect up to 1% of children. Pervasive developmental disorders are characterized by impairments in social skills, the communicative use of verbal and nonverbal language, and restricted and repetitive behaviors. Behaviors in the restricted and repetitive category share a focus on details and an inability to grasp concepts. Though it is not the focus of this review, it is important to appreciate that autism is a polygenic disorder with a heritability index of 0.90. The search for contributing genes has led to many promising but not yet replicated reports of associated genes. A recent study reported a significant genetic association between autism and a C allele in the promoter region of the MET receptor tyrosine kinase gene that codes for a protein that relays signals turning on a cell’s internal signaling cascades that can result in increased proliferation, motility, differentiation, process outgrowth, or survival. The strongest association occurred in families with more than 1 affected child. Inheriting 2 copies of this allele (the CC genotype) conferred a 2.27 relative risk of autism diagnosis and a 2-fold decrease in MET promoter activity and binding of transcription factor complexes. MET signaling is im-
important in neocortical and cerebellar development, immune system function, and gastrointestinal repair, all systems that have manifested signs of dysfunction in autism. Thus, this gene provides a mechanism for simultaneous multiorgan dysfunction in autism, compared with some theories that have hypothesized that immune system or gastrointestinal dysfunction causes brain dysfunction and thus autism. This study grew out of prior research implicating chromosome 7q31 as a candidate gene region and a cortical interneuron inhibitory hypothesis based on minicolumn abnormalities in autism that suggested a possible deficiency in interneurons. Such work exemplifies the translational research now possible as a result of cumulating research findings and the new mechanisms identified that have the potential to explain the complex array of findings in autism.

Autism is characterized by abnormalities in complex behavior, language, and cognition with mental retardation in 70% of cases and seizures in 30% of cases, and the absence of blindness, deafness, and long tract signs in 90% to 95% of cases without any cause for brain dysfunction other than autism. From a behavioral neuropsychology perspective, this constellation suggests generalized dysfunction of the association cortex, with sparing of primary sensory and motor cortex and of white matter. The absence of clinical signs of focal brain dysfunction common in children with hypoxic ischemic injury, such as visuospatial deficits and cerebral palsy, further suggests a distributed neural systems abnormality. The above behavioral neurological assessment was possible by the early 1980s, when secondary cases of autism were distinguished from idiopathic cases. However, it was not until the past 10 years that a neurobiology for autism matching this behavioral neurology emerged.

The contemporary neurobiology of autism began with evidence that group mean head circumference was at the 60th to 70th percentile relative to population norms and was disproportionate to height and weight. Fifteen percent to 20% of the autism group had macrocephaly (head circumference >99th percentile). Although larger head circumference for height was the most common outcome and true for the autism group as a whole, it was not universal; head circumference proportionate to height and head circumference less than height was also observed in autism. Thus, many head growth trajectories were consistent with autism. Head circumference data from very young children with autism retrospectively found onset of accelerated head growth by 12 months of age and macrocephaly in 15% to 20% of children by 4 to 5 years of age.

Structural magnetic resonance imaging studies confirmed the increase in total brain volume in autism, which had been inferred from the increased head circumference. The increase in total brain volume was documented beginning at 2 to 4 years of age, the earliest age of clinical recognition, and persisted into childhood but not adolescence. The tissues contributing to this increase were total cerebral white matter and total cerebral gray matter, with the latter contribution varying with the parcellation program used. One influential study of 6- to 11-year-old children parcellated cerebral white matter into an outer zone of radiate white matter composed of intrahemispheric corticocortical connections and an inner zone of bridging and sagittal compartments. The inner zone of white matter, especially the corpus callosum and internal capsule, showed no volume increase. The volume of the outer radiate white matter was increased in all cerebral lobes but with a frontal predominance. Collectively, these findings were interpreted as evidence of overgrowth of short- and medium-range intrahemispheric corticocortical connections with no detectable involvement of interhemispheric connections or connections between cortex and subcortical structures. The onset of brain overgrowth coincided with the onset of the signs and symptoms of autism, indicating that the overgrowth was part of a pathologic process that disrupted the development of normal brain structure and function in autism.

Another study examined cortical connectivity in an analogous way by comparing gyral and sulcal thicknesses as indices of short- and longer-distance cortical connections. This study found an overall increase in cortical thickness in a sample of high-functioning 8- to 12-year-old boys with autism compared with typical boys. Cortical thickness in sulci (long connections) was greater (analogous to increased volume of outer radiate white matter) than in gyri (short vertical connections), which is comparable to the findings of Herbert and colleagues for white matter.

A second consistent finding of cross-sectional imaging studies in autism has been a reduction in the size of the corpus callosum, though the segment affected has varied (D.L.W., unpublished data, 2006). In some studies, the decrease was only present relative to the increase in total brain volume in autism. In other studies, there was an absolute decrease in corpus callosum size independent of brain volume. The contrast between the increase in intrahemispheric white matter volume and the lack of change or decrease in corpus callosum size is notable, indicating that the neurobiological process affecting intrahemispheric white matter spares interhemispheric white matter. Although there is ample evidence of intrahemispheric processing deficits in autism, the sta-
onminicolumn abnormalities in autism. Prior to this, there were no substantive histopathologic abnormalities reported in the cerebral cortex in autism, though all behavioral neurologic evidence pointed to it as a primary site of brain dysfunction. Minicolumns are composed of radially oriented arrays of pyramidal neurons (layers II-VI), interneurons (layers I-VI), axons, and dendrites. Minicolumns assemble into macrocolumns, which form receptive fields. Minicolumns have been hypothesized to be the smallest radial unit of information processing in the cortex, but this function has not been confirmed. In autism, minicolumns have been reported to be increased in number and narrowed in width, with reduced neuropil space, with smaller neuron cell bodies and nucleoli (Figure 2). These abnormalities have been observed bilaterally in cortical areas 3, 4, 9, 17, 21, and 22. The description of these cortical abnormalities provided a critical counterbalance to the numerous reports of increased white matter volume, which might otherwise have led to a white matter model of autism. Second, the minicolumn abnormality provided a potential unifying link between gray and white matter abnormalities in autism, in that evolutionary evidence predicted an increase in white matter projections with an increasing number of minicolumns to maintain cortical connectivity. Diffusion tensor tracking data have documented an increase in pathway volume and fiber number even in the absence of increased total brain volume, eg, in adults with autism, thus providing evidence of the persistence of the predicted increase in fiber number (Figure 3). Because the narrowing of the minicolumns was largely related to a reduction in the neuropil space occupied by unmyelinated projections of γ-aminobutyric acid inhibitory interneurons, a deficit in cortical inhibition was hypothesized and proposed to explain the 30% prevalence of seizures, the sensory sensitivities, and the bias in information processing toward low-level perceptual processing. The reduction in inhibition was proposed to reduce the functional boundaries between minicolumns and bias toward encoding for details and the spread of excitation. Other types of studies described below have also hinted at a disturbance in cortical inhibition, suggesting that this mechanism may have validity in autism.

Additional evidence has also emerged to support cortical gray matter abnormalities in autism. A proton magnetic resonance spectroscopy study of 3- to 4-year-old children with ASD, with delayed development and with typical development found reduced choline compound concentrations and transverse relaxation, suggesting decreased cellularity or density in the cortex in the ASD children but not in the children with delayed or typical development. These magnetic resonance spectroscopy findings are consistent with the reported minicolumn abnormalities, given that 2- to 4-year-old children with ASD have increased total brain volume. The magnetic resonance spectroscopy findings for white matter were the same across groups, suggesting features common to delayed development. In a second study using a T2 relaxation measure (a measure of water content; its temporal progression is used as an index of brain maturation) in these same groups of children, T2 was prolonged in gray but not white matter in the ASD group but was prolonged in both gray and white matter in the developmentally delayed group. The selective involvement of gray matter in the ASD group was interpreted as evidence of abnormal developmental processes rather than delay as was concluded to be occurring in the developmentally delayed group in which gray and white matter were both affected.

There have been many remarkable contributions to the understanding of autism from functional magnetic resonance imaging (fMRI) studies. Individuals with autism have generally (but not always) been found to use similar cortical areas during cognitive processing as age-

Figure 2. Micrographs of Brodmann area 4, lamina III, from a patient with autism (A) and from an age-matched control (B). Insets highlight the cores of minicolumn fragments identified by a software program, illustrating the reduction in minicolumnar width in autism. Scale bars measure 200 μm in the full images and 50 μm in the insets. Image courtesy of Manuel Casanova, MD.

Figure 3. Cognitive pathway involved in face processing in typical adult subject (A) and in an adult with autism (B).
and IQ-matched controls. The most striking differences have been found in the patterns of activation and in the timing or synchronization of the activation across the cortical network recruited to perform different tasks. An initial fMRI study of written sentence comprehension indicated that high-functioning adults with autism had relatively higher levels of activation in the left posterior superior temporal gyrus (Wernicke) and relatively lower levels of activation in the left inferior gyrus (Broca) compared with age- and IQ-matched controls (Figure 4).\textsuperscript{18} In addition, analyses revealed striking reductions in functional connectivity or the correlation of the time series of the activation among cortical regions participating in performance of higher order tasks. Lower functional connectivity relative to the control group among participating cortical regions has been found in fMRI studies involving language,\textsuperscript{18,19} working memory,\textsuperscript{20} problem solving,\textsuperscript{21} and social cognition,\textsuperscript{22} providing evidence of a general problem with functional underconnectivity within and between neocortical systems in autism. Functional magnetic resonance imaging studies of object and face categories have reported evidence of atypical size and location of activation, suggesting that the boundaries of these areas are not normally defined and that cortical specialization may be atypical. Disturbances of this type suggest that the balance between inhibitory and excitatory neurons may be impacting cortical fields and cortical specialization in autism (K. Humphreys, unpublished data, 2006). Two of the fMRI studies reported that the functional connectivity measures of the autism group were correlated with the size of the genu of the corpus callosum, whereas no such relationship occurred for the age- and IQ-matched controls,\textsuperscript{19,21} supporting a relationship between functional and structural connectivity.

Another major fMRI contribution was the report of mirror neuron dysfunction as a potential underlying mechanism for the social-emotional deficits in autism.\textsuperscript{23} The mirror neuron system, pars opercularis in the inferior frontal gyrus, is active during the observation, imitation, and understanding of the intentions of others’ actions. It is therefore thought to provide a neural mechanism for understanding the actions and intentions of others. When acting in conjunction with the limbic system, it is further thought to mediate the understanding of emotions or the internal experience of another’s emotions so that the feelings of others are truly felt and understood at an emotional level, not just at a cognitive level (empathy). In the first study of the mirror neuron system in children with ASD compared with age- and IQ-matched typical children, the children with autism showed no mirror neuron activation in the pars opercularis during either observation or imitation of emotional face expressions. Furthermore, activation in this region was inversely related to their social domain scores on the Autism Diagnostic Interview (r = −0.85; P < .002) and the Autism Diagnostic Observation Schedule (r = −0.70; P < .02), the 2 measures that are used by researchers to verify the diagnosis of autism. The ASD children did exhibit increased activation in visual and motor areas. This activation was proposed to be compensatory. The authors suggested that early mirror neuron system dysfunction might be at the core of the social and emotional deficit in autism. Within the context of the connectivity model, it would appear that the connections between neural systems were not present to enable feelings to be connected to information.
Autism is conventionally defined by 3 symptoms or affected neural systems that co-occur for no apparent reason. The choice is to view these as separate dimensions coded for by different genes or to seek a common characteristic shared by the signs and symptoms that might explain their occurrence as a syndrome. Two studies examined the profile of neuropsychologic functioning in autism to identify a shared characteristic for the deficits and for the intact abilities.26,27 The first profile study provided the conceptual foundation for our fMRI studies that led to the present connectivity model for autism. As the field evolved, it was possible to also make the point with the second profile study that autism extended cognitively and neurologically beyond the diagnostic triad and thus more broadly involved the brain. Testing of 178 high-functioning autistic and control individuals aged 8 to 40 years across both studies revealed deficits in higher cortical sensory perception, skilled motor abilities, memory for complex stimuli that required detection or application of an organizing strategy, higher order language abilities (detection or creation of story themes, metaphors, inferences, or idioms), and concept formation. Sparred or enhanced abilities included attention, elementary sensory perceptual abilities, elementary motor skills, memory for simple material dependent on basic associative skills, formal language skills, and the rule-learning aspects of abstraction. The conclusions drawn from this pattern were that (1) basic information acquisition abilities were intact, (2) impaired abilities shared a dependence on high demands on processing information or integration, (3) intact abilities shared a dependence on low information-processing demands, and (4) within and across domains, skills or abilities were impacted in proportion to the demands for integration of information. These observations led to the proposal that autism was a disorder of complex information processing with intact or enhanced simple information processing.28 This construct provided a reasonable account for the co-occurrence of the signs and symptoms as a syndrome. It was also a valuable model for intervention and teaching. From a neurobiological perspective, this concept suggested a developmental disturbance in neuronal organizational events with preservation or overdevelopment of local circuitry and underdevelopment of the connections within and between cortical systems in high-functioning individuals with autism. In low-functioning individuals with autism, there appears to be little to no development of functional connections between primary sensory cortex and association cortex. The common themes across the spectrum, regardless of severity, are cortical connectivity and information-processing capacity.

A second major implication of the neuropsychologic profile studies was that domains outside the classic diagnostic triad were involved. Previously, sensory and motor manifestations were considered associated signs and symptoms, and memory dysfunction (other than the disproved amnesia hypothesis) was not thought to be part of autism. However, the involvement of these areas of function in the same pattern as the traditional signs and symptoms implied that these domains were impacted by the same neurobiologic process and that autism had a far broader impact on the brain than was originally conceptualized. This conclusion was reinforced by a large study of postural control from childhood to middle age in autism, which revealed delayed onset of maturation of postural control with failure to achieve adult levels of function.20 The postural instability was the result of reduced capacity for multimodal sensory integration (visual, vestibular, and position sense). This study provided timely support for the emerging connectivity model of autism but also for the concept that autism broadly affected the brain, with information integration as a common denominator.

Another not well-appreciated aspect of this clinical syndrome is the second wave of deficits that emerges in the second decade of life. Frontal circuitry normally matures during this time period, and oculomotor, fMRI, and neuropsychologic studies of working memory and executive function in autism have revealed the emergence of new deficits in adolescence in autism, with the failure of frontal lobe skills to develop.20 Previously, it was thought that adolescents and young adults with autism fell further behind peers in adaptive function in the second decade because life became more challenging. In fact, the higher order frontal lobe skills needed to cope with these life demands failed to develop in autism. This severe frontal dysmaturity likely accounts for the unexpectedly poor adaptive function in adult life in the majority of high-functioning ASD individuals.

The structural imaging findings have led to the near general acceptance of autism as a disorder originating in the brain rather than in behavior, a subtle but significant distinction. (Social theories hold that lack of motivation to interact is the initiating event in autism and results in failure of brain circuitry to develop. Thus, the underdevelopment of fusiform face area is secondary to the lack of eye contact, rather than underdevelopment of the circuitry for nonverbal language and fusiform face area being a primary event that results in the observed behavior.) Developmental alterations in white matter and their role in altered intrahemispheric connectivity reflect a new understanding of the involvement of white matter in childhood disorders and a departure from the traditional injury model (cerebral palsy). These findings, together with fMRI studies, have shifted thinking away from autism as a disorder of regional brain dysfunction to a model of autism as a large-scale neural systems disorder with alterations in cortical systems connectivity. Recent findings have also implicated cerebral gray matter, creating a picture of disturbances in cerebral gray and white matter connectivity. Studies also suggest that abnormalities in cortical synchronization and in the balance of cortical inhibition and excitation may be mediating mechanisms. Various genetic mechanisms are beginning to be identified to account for not only multigene involvement but also the diversity of the findings within the central nervous system.

The limitations of this review are many. Most notable is the failure to touch on the richness of the literature related to the social, emotional, gaze, face-processing, and motion-processing or motion detection networks and their associated cognitive and neurologic implications for autism. Genetics, epigenetics, epidemiology, developmental neurobiology, neurochemistry, and mouse model contributions have also been neglected.
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Correction

In the article titled “The New Neurobiology of Autism: Cortex, Connectivity, and Neuronal Organization” by Minshew and Williams, published in the July 2007 issue of the Archives (2007;64[7]:945-950), Figure 4A was mislabeled. The labels LSTG and LIFG should be switched, with LIFG on the left and LSTG on the right.