Genetics of Childhood Disorders: XLIII. Autism, Part 2: Neural Foundations

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Autism is a severe developmental disorder marked by significant impairments in social, behavioral, and communicative functioning. Its early onset, symptom profile, and chronicity strongly argue for a biological basis, and in fact, several of lines of research implicate core biological mechanisms. For example, autism is one of the most strongly genetic conditions, and preliminary linkage data have already identified susceptibility regions likely to contain genes involved in the condition. About a quarter of individuals with autism exhibit a seizure disorder, and a larger number of individuals have abnormal EEGs, which typically indicate bilateral abnormalities without a consistent focus. However, the absence of consistent biological markers presents across all cases and the pronounced heterogeneity of the manifestations of autism have slowed research into its pathophysiology.

And yet, major progress is being accomplished following the advent of new tools of biobehavioral research. Novel neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are beginning to map out the neural systems affected by autism. These include brain areas responsible for emotional and social functions, per-

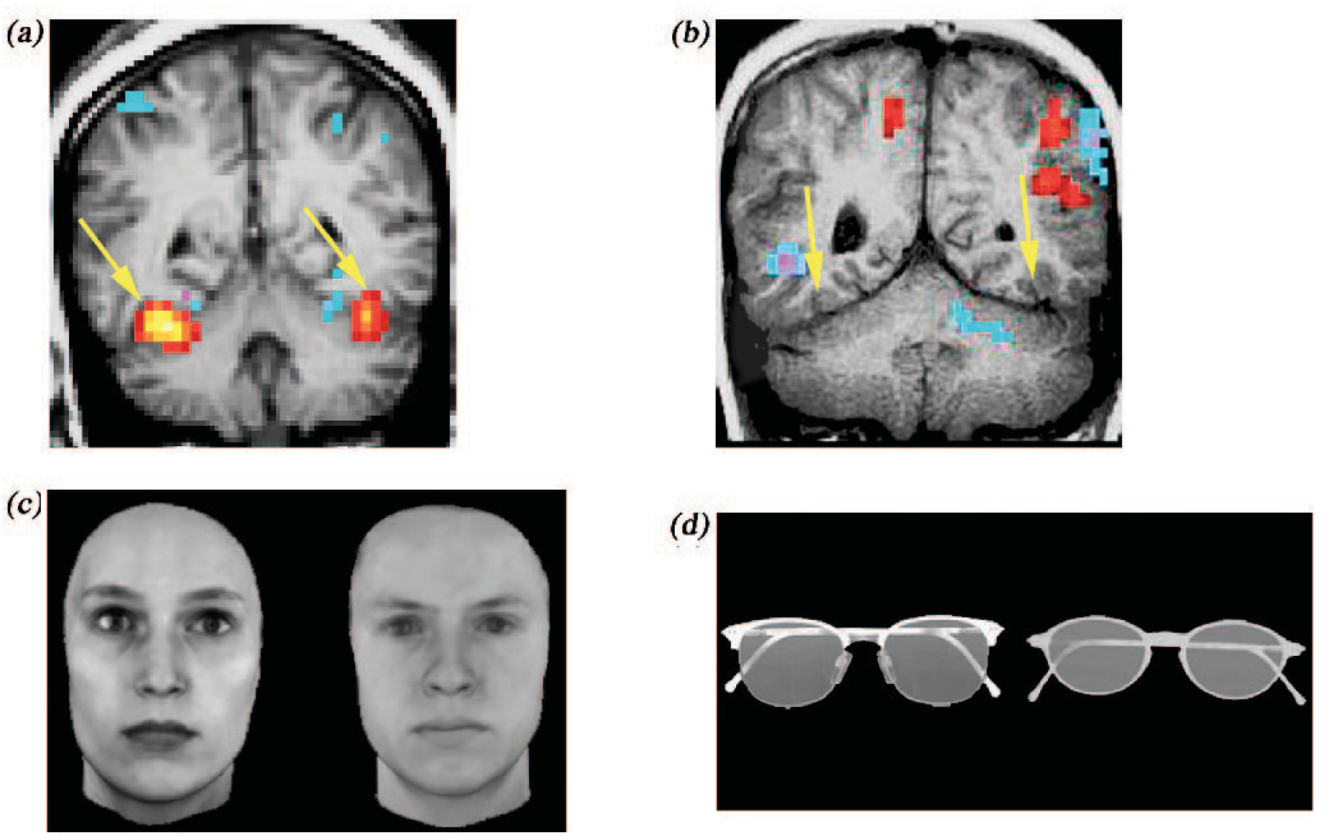

Fig. 1 Functional magnetic resonance imaging (fMRI) t-maps of the brain during face perception. The fusiform face area is shown in red/yellow (arrows) in (a) a young adult with autism and (b) a matched normal control subject. In the control subject, there is a clear focus of face-related activation bilaterally in the fusiform gyrus along the ventral surface of the temporal lobe. Contrast this with the lack of activation in the fusiform gyrus in a young adult with autism. Images are in a coronal orientation, with right and left hemisphere reversed by convention, and functional data are superimposed on anatomical images for localization. fMRI data are from a blocked experiment comparing (c) face perception to (d) nonface object perception during a "same/different" discrimination task on a 1.5-Tesla system; the threshold for displaying activations is set at T = 1.5. Object-specific areas are shown in blue on the fMRI maps.

ceptual systems specific to face and affect recognition, and social-cognitive systems involved in understanding the intentions of others. Working models of the pathophysiology of autism commonly include the amygdala at the center of a distributed cortical-subcortical system, but other competing models exist.

The social, language, and behavioral problems that occur with autism suggest that the syndrome affects a functionally diverse and widely distributed set of neural systems. At the same time, however, the affected systems must be discrete, because autism spares many perceptual and cognitive systems. For example, autism is not incompatible with normative intelligence or even superior visual-perceptual and other neuropsychological skills and talents. Even though the full syndrome likely involves insults to multiple systems, it remains possible that the initial insult is localized, branching off into more pervasive impairments because of the highly interdependent nature of early developmental processes.

Nearly every neural system in the brain has been proposed at some point as the cause of autism. Currently, the research data suggest that select aspects of the temporal and frontal lobes, and portions of the amygdala, are key nodes in systems affected by autism. Underlying the challenges to the research effort is the fact that mental retardation is present in about 70% of individuals with autism, forcing researchers to disentangle causative processes that are specific to autism from the nearly ubiquitous confound of cognitive disability.

One of the more intriguing findings to emerge in the past few years is that overall brain size appears to be increased in autism (by about 5%–10%). It is not yet understood whether all brain regions and systems are equally affected by the expansion or whether this finding applies to all levels of cognitive functioning. There is also some variability in the size of the effect with age; some studies suggest that the enlargement is especially pronounced in childhood, perhaps affecting white matter more than gray matter. Whole brain enlargement could be merely a marker for a disturbance in the fine structure of the brain that actually causes autistic symptoms. Increased brain size might come at the expense of interconnectivity between specialized neural systems, giving rise to a more fragmented processing structure. In fact, some evidence suggests that the corpus callosum, the major fiber pathway between the hemispheres, is reduced in size in autism. Moreover, one PET study found a reduction in coordinated brain activity. Less neural integration would be consistent with one influential theory that attributes autistic symptoms to a lack of "central coherence," a cognitive processing style that makes integration of parts into wholes problematic. One study measuring EEG gamma-band bursts associated with the process of "perceptual binding" in individuals with autism lends further support to this hypothesis.

Debate continues as to whether the growth abnormality is postnatal or prenatal. Specifying the developmental epoch with the most abnormal growth rate would provide better clues to the underlying mechanism. An origin at particular times of fetal brain development could suggest, for instance, disturbances in the regulation of neuronal or glial cell proliferation, neuronal migration, or apoptosis (programmed cell death). Prenatal origins of disturbed brain development have been suggested by studies finding an increased frequency of morphological abnormalities of the cerebral cortex in autistic individuals (e.g., regional alterations in the size and number of gyri). Such abnormalities stem from disturbances in neuronal migration during fetal brain development. These gross neuroanatomical abnormalities are much more common among autistic individuals with mental retardation in contrast with those with normative IQs, and still they occur only in a minority of cases. Thus these findings do not appear to be specific to the core social deficit in autism.

Postmortem studies of a small number of persons with autism have revealed a range of abnormalities, including a significant decrease in the number of Purkinje cells and granule cells in the cerebellum. The precise nature of these abnormalities, including a lack of gliosis indicative of scarring, suggests a prenatal origin. A focus on the cerebellum would be consistent with some neuroimaging evidence. A variety of posterior fossa abnormalities seen on MRI have been reported in autism. These include abnormalities of the pons, fourth ventricle, and cerebellar vermis, the midline portion of the cerebellum. One influential set of findings ties autism to hypoplasia of the neocerebellar vermis, but this abnormality has not consistently been observed across studies. Moreover, it seems likely that posterior fossa abnormalities are not specific to autism, but rather evident in many persons with developmental disabilities and mental retardation. Thus specificity of the findings for the core autistic features seems doubtful.

Of the specific brain regions implicated in the pathobiology of autism spectrum conditions, none has attracted as much interest as the limbic system, especially the amygdala and its functional partners in the temporal and frontal cortices. The limbic system lies largely within the medial and ventral region of the temporal lobe, providing a girdle around the phylogenetically older, deep brain structures. The amygdala, in particular, plays a critical role in emotional arousal, assigning significance to environmental stimuli and mediating the formation of visual-reward associations or "emotional" learning. The amygdala has many afferent and efferent connections to the temporal lobe, forming an important system for mediating the perception of social stimuli.

Postmortem examination of the brains of persons with autism finds consistent evidence for abnormalities in size, density, and dendritic arborization of neurons in the limbic system, including the amygdala, hippocampus, septum, anterior cingulate,

and mammillary bodies. There is a stunting of neuronal processes and increased neuronal packing density, suggesting a curtailment of normal development. These affected regions are strongly interconnected, and together they comprise the majority of the limbic system. The limbic system, especially the amygdala, is part of a neural structure that supports social and emotional functioning. These postmortem findings, therefore, are often heralded as the first good entrance points for understanding the pathobiology of the autism spectrum disorders.

There is supportive evidence for an amygdala theory of autism from animal models of autism created through the lesioning of the amygdala of monkeys shortly after their birth. Gradually in the course of the first year of life, these animals develop patterns of behavior reminiscent of autism, i.e., social isolation, lack of eye contact, expressionless faces, and motor stereotypies. Similar lesions in adulthood fail to produce autistic-like sequelae. These findings are consistent with the notion that autistic symptoms are in part a function of faulty early emotional learning mediated by limbic system pathology. Moreover, as monkeys with early lesions to the amygdala and surrounding entorhinal cortex mature into adulthood, additional abnormalities are found in the neurochemistry of the frontal cortex and in the subcortical regulation of dopaminergic activity. Thus early discrete damage can produce widespread abnormalities across development.

Persons with autism have deficits in their ability to recognize and discriminate faces and to understand facial expressions. Functional neuroimaging and lesion data show that the fusiform gyrus, a region on the underside of the temporal lobe, is normally an area for face perception, while neighboring regions in the posterior regions of the middle and superior temporal gyri are important for reading facial expressions and social intent through eye-gaze direction. Several functional MRI (fMRI) studies have now shown hypoactivation of the fusiform gyrus during face perception tasks (Fig. 1). In a short period of time, this has now become the best replicated finding in the neuroimaging literature. Preliminary evidence also links hypoactivation of the amygdala and lateral temporal cortices to autism. One hypothesis is that the principal pathology in autism resides in limbic regions and that disturbance in social-affective orientation early in life causes a cascade of neurodevelopmental events, including failure to develop perceptual competence for faces and for visual and auditory displays of emotion. The corollary of this hypothesis is that deficits in subsequent and more complex social-cognitive skills may result from this early derailment of the socialization processes.

Aspects of frontal lobe integrity and function have been implicated in the pathogenesis of autism. Older studies using lower-resolution neuroimaging techniques reported general hypoactivation of the frontal lobes. Functional neuroimaging data collected in the past decade are converging to show that subregions of the prefrontal cortices with especially strong connectivity to limbic areas are critical for "social cognition," i.e., thinking about others' thoughts, feelings, and intentions. Deficits in such "theory of mind" abilities are common in autism. Theory of mind ability has been linked to functional activity in the medial region of the superior frontal gyrus (primarily Brodmann area 9) and to the prefrontal cortex immediately above the orbits of the eyes (i.e., orbital frontal cortex). Bilateral lesions to the orbital and medial prefrontal cortices cause deficits on theory of mind tasks. Preliminary functional imaging evidence in autism spectrum conditions suggests altered functional representation in the prefrontal cortex regions during theory of mind tasks. Moreover, medial prefrontal dopaminergic activity as measured by fluorine-18-labeled fluorodopa PET has been found to be significantly reduced in autism. Reduced glucose metabolism during memory activities has also been reported in a subdivision of the anterior cingulate gyrus, a region that lies along the medial surface of the frontal lobe. Moreover, nonhuman primate studies have documented abnormal social responsivity and loss of position within the social group following lesions to the orbital and medial prefrontal cortices.

The orbital and medial prefrontal cortices have dense reciprocal connections with the amygdala, providing the architecture for a system that can regulate social-cognitive processes. A parallel set of amygdala-cortical circuitry in the temporal lobes focuses on social-perceptual processes. One hypothesis is that autism is largely caused by abnormalities in both of these amygdala-cortical loops.

The major findings to date on the neural basis of autism involve abnormalities in brain size, aspects of the limbic system, functionally related and connected regions of the orbitomedial prefrontal cortex, and visual association areas of the temporal lobe. While good progress toward understanding the neural basis of autism has been made in recent years, much work still needs to be done. In this context, fMRI is revolutionizing psychiatry and systems-level neuroscience, and it ultimately should enable researchers to define dynamic brain processes that give rise to each specific symptom and feature of autism. The closer synergy attained in the past few years between more refined behavioral methods developed to isolate core aspects of social processing and co-registered functional neuromapping further increases the promise of this effort. A challenge for research in this area will be to adapt in vivo neuroimaging techniques so that they are applicable to the developing infant and toddler. Studying younger children may be a prerequisite for a comprehensive understanding of the neural basis of autism because the disorder evolves into its full form in a rather short period of time in the first 2 years of life. Moreover, the initial derailment of fundamental socialization processes is likely to unleash a wide range of anomalous experiences that, in turn, are likely to result in lifelong neurostructural and neurofunctional abnormalities.

WEB SITES OF INTEREST

Yale Developmental Neuroimaging Program: http://noodle.med.yale.edu/dnp/
McDonnell Foundation Perceptual Expertise Network: http://WWW.PSY.VANDERBILT.EDU/faculty/gauthier/PEN/index.html
Yale Child Study Center Autism Program: http://www.info.med.yale.edu/chldstdy/autism/index.html
Human Brain Mapping Org: http://www.humanbrainmapping.org/

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