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Autism and Abnormal Development of Brain Connectivity

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It has been said that people with autism suffer from a lack of "central coherence," the cognitive ability to bind together a jumble of separate features into a single, coherent object or concept (Frith, 1989). Ironically, the same can be said of the field of autism research, which all too often seems a fragmented tapestry stitched from differing analytical threads and theoretical patterns. Defined and diagnosed by purely behavioral criteria, autism was first described and investigated using the tools of behavioral psychology. More recent years have added brain anatomy and physiology, genetics, and biochemistry, but results from these new domains have not been fully integrated with what is known about autistic behavior. The unification of these many levels of analysis will not only provide therapeutic targets for prevention and remediation of autism but can also provide a test case for theories of normal brain and cognitive development. Autism research therefore has much to learn from and much to offer to the broader neuroscience community.

Clinical features

Clinically, autism is defined by a "triad" of deficits comprising impaired social interaction, impaired communication, restricted interests, and repetitive behaviors. Although in some cases speech never develops fully or never develops at all, in other cases, speech may be present but so inflexible and unresponsive to context that it is unusable in normally paced conversation; often, speech is limited to echolalia or confined to narrow topics of expertise in which discourse can proceed without conversational interplay. The communicative impairment extends also to nonverbal signals such as gaze, facial expression, and gesture. Social behaviors, too, are beset by a lack of flexibility and rapid coordination: children with autism do not coordinate attention between objects of mutual interest and the other people who may be interested in them, often engage in "parallel play" at the edge of a group rather than joining in cooperative play, and do not engage in pretend play. Intense and narrowly focused interests tend to concentrate on systems (Baron-Cohen, 2002) that operate deterministically and repeatably according to tractable sets of rules, whether these are abstract and complex systems such as computers or role-playing games or very concrete and simple systems such as toilets or washing machines. Critical to identifying the causal factors of autism, and key to its relevance to normal development, is the recognition that autism is actually the extreme of a spectrum of abnormalities. Milder phenotypes on this spectrum include Asperger syndrome (Wing, 1981) in which language is relatively unimpaired, and the "Broader Autism Phenotype" in which characteristic cognitive traits are present subclinically (Dawson et al., 2002). The combination of this broad variation of phenotypes and a 60–90% concordance rate in identical twins (Bailey et al., 1995) suggests a large number of genetic and environmental biasing factors (Muhle et al., 2004).

A basis in neural connectivity?

In addition to the central coherence paradigm, autism has been variously characterized as a deficit of executive function (Ozonoff et al., 1991), complex information processing (Minshew et al., 1997), theory of mind (Baron-Cohen et al., 1985), and empathy (Baron-Cohen, 2002). Each of these theories is a valid description of many aspects of the autistic syndrome but each, in answering unsolved questions at one level of explanation, introduces them at another. Recent attempts at a theoretical synthesis have focused on abnormal neural connectivity, and, superficially, there seems some disagreement as to whether this abnormality involves a surfeit (Rubenstein and Merzenich, 2003; Belmonte et al., 2004) or a deficit (Brock et al., 2002; Just et al., 2004) of connectivity. The picture is complicated by the fact that the term "connectivity" admits more than a single meaning. Conceptually, we can differentiate local connectivity within neural assemblies from long-range connectivity between functional brain regions. On another axis, we can also separate the physical connectivity associated with synapses and tracts from the computational connectivity associated with information transfer. Physically, in the autistic brain, high local connectivity may develop in tandem with low long-range connectivity (Just et al., 2004), perhaps as a consequence of widespread alterations in synapse elimination and/or formation (Sporns et al., 2000). Furthermore, indiscriminately high physical connectivity and low computational connectivity may reinforce each other by failing to differentiate signal from noise (Rubenstein and Merzenich, 2003; Belmonte et al., 2004) (Fig. 1). This model is consistent not only with the impairments in higher-order cognition described by the diagnostic triad but also with impairments of motor coordination (Teitelbaum et al., 1998), perceptual abnormalities such as high visual motion co-

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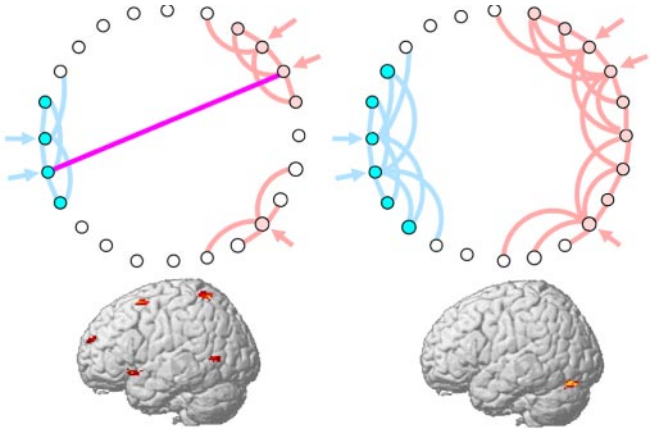

Figure 1. Potential effects of network connectivity patterns on brain activation. In the network on the left, a combination of strong local connectivity within delimited groups of neural units and selective long-range connectivity between local groups constitutes a computational structure within which information can be efficiently represented and efficiently propagated. Inputs (double arrows) evoke representations that are easily differentiable from noise (single arrow) and can be linked across regions, yielding high computational connectivity. In the network on the right, strongly connected subregions are not appropriately delimited and differentiated, and computationally meaningful long-range connections fail to develop. The brain images at bottom, from a visual attention task, display distributed patterns of functional activation in the normal brain (left) and abnormally intense and regionally localized activation in the autistic brain (right), a pattern that may stem from such differences at the network level.

herence thresholds (Milne et al., 2002) and broad tuning of auditory filters (Plaisted et al., 2003), abnormal growth within regions of local but not long-range white-matter projections (Herbert et al., 2004), and the substantial comorbidity of epilepsy with autism (Ballaban-Gil and Tuchman, 2000).

Functional anatomy in an abnormally wired brain

How can we test and refine this model of reduced information transfer as a consequence of local overconnectivity and long-range underconnectivity? One experimental approach is the physiological study of attention in autism using methods such as functional magnetic resonance imaging (fMRI) and evoked potentials. In an overconnected network, sensory inputs should evoke abnormally large activations for attended and unattended stimuli alike, giving rise within sensory regions to an overall increase in activation but a reduction in the selectivity of this activation, and potentially incurring a high load at later stages of perceptual processing as distractors are differentiated from targets. Conversely, brain regions subserving integrative functions will be cut off from their normal inputs and should therefore manifest reductions in activation and in functional correlations with sensory regions. A combination of EEG (Belmonte, 2000) and fMRI (Belmonte and Yurgelun-Todd, 2003) measures in a task of visual spatial attention demonstrates exactly this pattern. Furthermore, new data suggest abnormally strong activation in parietal cortex during suppression of distractors, at the same time as integrative regions in prefrontal and medial temporal cortices are abnormally quiescent (Belmonte and Baron-Cohen, 2004). Non-autistic brothers of people with autism seem to share the prefrontal and medial temporal hypoactivation but not the posterior hyperactivation, suggesting that low activity in integrative brain regions may be an endophenotype reflecting familial patterns of brain organization that may place individuals at heightened risk for autism.

The cerebellum and development of abnormal connectivity

Particularly implicated in deficits of long-range connectivity and coordination of cognitive functions is the cerebellum, one of the most common sites of anatomic abnormality in autism (Courchesne, 1997; Courchesne and Pierce, 2002). MRI morphometry reveals hypoplasia of the cerebellar vermis and hemispheres, and autopsy studies report reductions in numbers of cerebellar Purkinje cells. Moreover, recent genetic (Gharani et al., 2004) and MRI-behavior correlation (Akshoomoff et al., 2004; Kates et al., 2004) studies suggest that cerebellar abnormality may play a more central role in autism than previously thought. Neurobehavioral studies have shown associations between cerebellar anatomic abnormality and certain motor, cognitive, and social deficits (Haas et al., 1996; Harris et al., 1999; Townsend et al., 1999; Pierce and Courchesne, 2001).

Functionally, in autism, cerebellar activation is abnormally low during a task of selective attention (Allen and Courchesne, 2003) and abnormally high during a simple motor task (Allen et al., 2004). Both of these functional abnormalities correlate significantly with reduced size of cerebellar subregions, and it seems likely that this structure–function correspondence extends to the microscopic level and in particular to the reduction in Purkinje cell numbers. Such a reduction would release the deep cerebellar nuclei from inhibition, producing abnormally strong physical connectivity and potentially abnormally weak computational connectivity along the cerebello-thalamocortical circuit. This altered pattern of cortical excitation may produce aberrant activity-dependent patterning and may thus be related to findings of abnormal individual variability in cortical maps for motor function (Müller et al., 2001) and face processing (Pierce et al., 2001) and to abnormal overgrowth in frontal lobes (Carper and Courchesne, 2000).

Coordinated brain activity and the development of temporal binding

fMRI can capture inter-regional correlations on a timescale of seconds, but what about neural connectivity on a shorter timescale? Brock et al. (2002) proposed that underconnectivity between separate functional brain regions in autism might be reflected in a lack of EEG synchrony in the gamma band (30–80 Hz). In normal subjects, gamma activity is modulated by a variety of integrative processes, including feature binding (Tallon-Baudry et al., 1998), top-down feature selection (Hermann and Mecklinger, 2001), attention (Müller et al., 2000), face processing (Keil et al., 1999; Rodriguez et al., 1999), emotional arousal (Keil et al., 2001), and memory rehearsal (Tallon-Baudry et al., 1998, 1999). We are in the process of testing Brock's hypothesis using a delayed match-to-sample task, and preliminary data suggest abnormality of gamma activity over frontal cortex and visual processing areas during both stimulus encoding and memory rehearsal. Decreased and/or delayed gamma activation would suggest disrupted neural signaling and would support the hypothesis of abnormal regional activation patterns.

Linking altered structure and function with altered neural development

Neuropathological studies of cerebral cortex in autism indicate abnormalities of synaptic and columnar structure (Williams et al., 1980; Casanova et al., 2002) and of neuronal migration (Bailey et al., 1998a). MRI morphometry in young children with autism reveals excessive volume of cerebrum or cerebral white matter (Courchesne et al., 2001; Sparks et al., 2002; Herbert et al., 2003) or increased total brain volume (Piven et al., 1995; Aylward et al.,

2002). The absence of such a volume difference in adults (Courchesne et al., 2001; Aylward et al., 2002) suggests that early hyperplasia in autism is followed by a plateau during which brain growth in normal subjects catches up. Retrospective analyses of head circumference measurements suggest that much of the overgrowth occurs postnatally within the first 6–14 months (Courchesne et al., 2003), coinciding with what is normally a period of exuberant synaptogenesis, dendritic arborization, and ongoing myelination. Regionally, frontal lobes show the greatest degree of enlargement and occipital lobes the least (Carper et al., 2002; Piven, 2004), and, within the frontal lobe, the dorsolateral convexity shows significant overgrowth, whereas precentral gyrus and orbital cortex are not robustly affected (Carper and Courchesne, 2004). Thus, the cortical areas most affected are precisely those broadly projecting, phylogenetically and ontogenetically late-developing regions that are essential to complex cognitive functions such as attention, social behavior, and language.

Fragile X syndrome and autism: are there common mechanisms in the development of synaptic connectivity?

The early developmental timing of brain overgrowth in autism, the neuropathological indications of altered synaptic structure, and the considerable dependence on genetics are especially interesting in light of the presence of autistic behavior in fragile X syndrome (FXS), a disorder with a known genetic cause and substantial symptomatic overlap with autism. Approximately one-quarter to one-third of people with FXS show the symptoms of autism (Bailey et al., 1998b; Rogers et al., 2001). FXS is caused by the silencing of a single gene (*FMR1*) (Pieretti et al., 1991) that codes for the fragile X mental retardation protein (FMRP), an RNA binding protein (Ashley et al. 1993) whose absence presumably alters expression of the genes associated with its mRNA cargoes. Thus, although FXS is in one sense a single-gene disorder, it is more proximally the result of disruption of complex patterns of expression of many genes, genes that may likewise be abnormally expressed in autism. Examinations of gross neuroanatomy as well as neuronal morphology in FXS have revealed specific structural alterations (for review, see Beckel-Mitchener and Greenough, 2004). Dendritic spines in specific cortical regions are present at high density and are abnormally long and thin, suggesting an immature morphology that may produce overconnectivity. Although large-scale, parallel studies with autistic brains are lacking, decreased dendritic branching in the hippocampi of two postmortem autistic brains (ages 7 and 9) (Raymond et al., 1996) suggests a reduction in connectivity. Additional work in autism is necessary to characterize neural structure across anatomical regions and developmental periods and to evaluate the possible roles of FMRP-associated genes.

Immune signaling in normal brain development and plasticity: implications for autism

One possible point of convergence between genetic and environmental causal factors in autism is immunological challenge. Autism and the immune system have been linked genetically and symptomatically (Warren et al., 1996; van Gent et al., 1997; Krause et al., 2002). Recent studies have shown that normal neurons in developing and adult brains express proteins of the major histocompatibility complex (MHC) class I, known for their role in the immune system (Corriveau et al., 1998; Huh et al., 2000). Furthermore, these immune proteins are required for specific forms of developmental and functional plasticity, demonstrating that changes in MHC expression can lead to neurodevelopmental defects. Interestingly, maternal viral infection at midpregnancy has been called "the principal nongenetic cause of autism" (Ciaranello and Ciaranello, 1995). Cerebellar Purkinje cells, which are reduced in autism, are a site of striking MHC class I expression. Decreased expression of MHC class I impairs the pruning of inappropriate synaptic connections (Huh et al., 2000), an effect that may explain the early developmental increase in brain volume in autism and the symptomatic overlap with FXS. A possibility currently being investigated is that specifically timed changes in neuronal MHC class I expression contribute to the development and/or expression of autism.

Conclusion

We have presented abnormal neural connectivity as an explanatory framework within which genetic and neuropathological findings on autism may be unified with neuroanatomy, neurophysiology, and behavior. Communication between these levels of analysis promises a greater understanding of mechanisms underlying both normal and pathological development of neural and cognitive systems and has the potential to render a multiplicity of experimental and theoretical approaches more coherent.

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