

Neural Mechanisms in Autism¹

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Currently, there is no reliable evidence as to exactly what are the neural bases for autism. There are no accepted genetic markers, even though there are several candidates (Bailey, Palferman, Heavey, & Le Couteur, 1998; Folstein, Bisson, Santangelo, & Piven, 1998; Szatmari, Zwaigenbaum, & MacLean, 1998). It is also increasingly clear that autism is a heterogeneous disorder, even if it is genetic. There are no objective tests *in vivo* that are specific for the condition. There have been no structural, metabolic, or neuropathologic abnormalities that have been reliably linked to autistic features. There is no accepted animal model of the condition, although infant monkeys with selective brain lesions (Bachevalier, 1991; Bachevalier & Merjanian, 1994) show behavioral features suggestive of autism.

NEUROBIOLOGIC STUDIES

Although no neuropathologic features have been found yet to be characteristic of autism, a number of abnormalities have been reported. Bauman and Kemper (1994) found consistent neuronal changes (“too many, too small”) in the hippocampus, amygdala, and other areas of the limbic system, as well as decreased Purkinje cells in the lateral cerebellum. More recently, Bailey et al., (1998) reported cerebellar, neocortical, and olivary

(but not limbic) changes. These findings may reflect “developmental curtailment” of the cellular connections in the developing cortex (neuropil) that affects information processing and representational memory (in the hippocampal complex); recognition of facial gestures and cross-modal memory (amygdala); and shifting attention, language processing, and motor function (cerebellum). In spite of the limitations of traditional methods inherent in light microscopic studies of autism so far (Rapin & Katzman, 1998), and the paucity of postmortem tissue available for study, these studies have fostered a new era in neurobiological research in autism by other investigators who are using recently developed genetic, neurochemical, and morphological techniques.

Diverse Causes for Similar Defects of “Higher Cortical Functions”

Autism can be caused by a number of different insults and etiologies. These causes may be as diverse as viral infections, dysmorphic syndromes, or genetic abnormalities of intracellular metabolism. In any individual,

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these would produce a fairly unique pattern at the neural level, even though their behavioral outcomes are more similar. There are some aspects of function in which it is possible to make a fairly direct correlation to neuroanatomy, particularly in the fully developed organism. The elementary sensory and motor systems are the best examples. However, higher cognitive abilities, by their very nature, are the product of a number of different underlying mental functions. Each of these functions may have very complex relationships to neural structures. These mental functions may not even be products of structures *per se*, as much as of their internal dynamics or the dynamics of other systems and structures. Moreover, many of the functions considered to be *higher* abilities are actually *chains* of abilities that unfold over time. The higher functions considered to be most important were unlikely to have sprung up full-blown in phylogeny. More likely, they have been cobbled together out of refined and rearranged combinations of other functions. Therefore, such functions may not have very direct brain correlations. The situation is even more complicated in the case of developmental disorders. Normal mental development proceeds through a cascade of many different processes, which tend to bootstrap each other. The interruption, or just simple delay, in any part of this sequence, can and often does have major effects on the final components and their assembly into a functional whole.

The genetic deficits of autism may be expressed in peculiar patterns that can be related to neurobiologic organization, but not to the functional organization of the nervous system. They also may be expressed at different times in the developing nervous system. Some of these effects may be visible at the time they occur, whereas some may take a long period of subsequent development to be expressed. It is still a reasonable strategy to look as early in

development as possible for clues to the neurobiologic problems. A recent example is the study by Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer (1998), which showed that movement disorders could be retrospectively detected in autistic children as early as ages 4 to 6 months. Of particular relevance to the issues raised here is that the movement disorders were expressed in different movements, and in different ways, among the different children.

Neural Networks

Neuropathological findings in the limbic system, cerebellum, and frontal cortex in autism suggest that disorders in these structures may be important contributors to the autism deficit. Variations in clinical expression among autism spectrum disorders may relate to different types of effects—as well as their distribution—in related structures, such as the basal ganglia (important for motor planning) and prefrontal cortex (motivation, executive functions) (see Figure 1). These regions may be dysfunctional by themselves (e.g., following closed-head injury, stroke, or encephalitis) or may become disconnected from their interactive partners within networks due to their failure to develop, modify, or prune their connections during development of the neuropil (Zilbovicius et al., 1995). For example, the basal ganglia (caudate and globus pallidus) and thalamus are essential subcortical integrating way-stations in networks with prefrontal and anterior cingulate cortex. Abnormalities in subcortical neurotransmission to or from the prefrontal cortex are likely to contribute to executive dysfunction, disinhibition and irritability, and apathy and inertia (Denckla & Reiss, 1997).

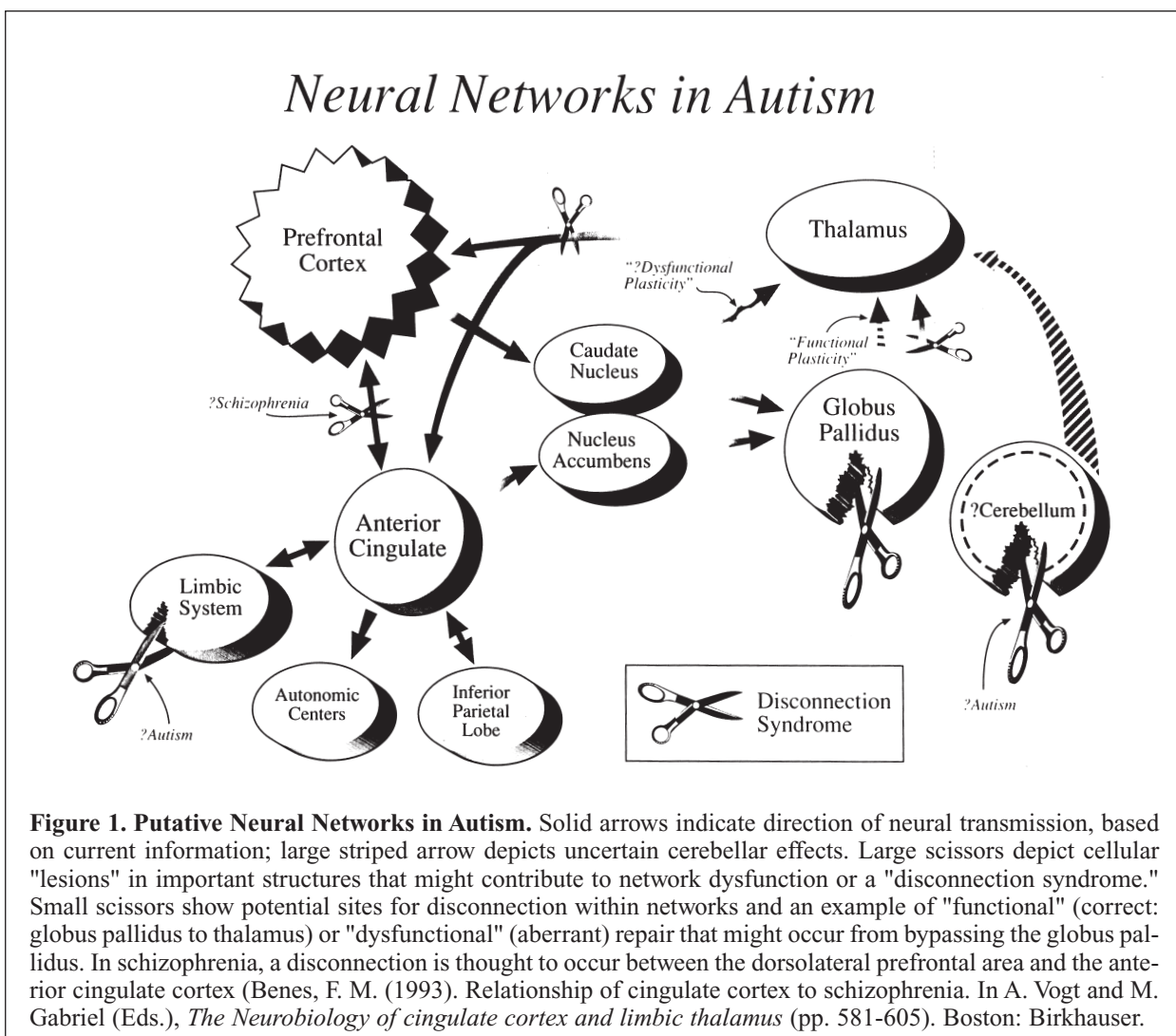
The capacity for repair of, or compensation for, brain lesions (plasticity) is maximal during the early years of development (Jacobson, 1991). Therapeutic programs in

autism may take advantage of this potential for repair (Greenspan & Wieder, 1997; Lovaas, 1987). Although its biological basis is poorly understood, clinically effective repair may depend on the regulation of multiple neurotransmitters, growth, and other trophic factors in the brain while training programs are taking place. (Repair also may occur to some degree with or without training.) Compensation for defective way-station processes (e.g., hippocampal or cerebellar), or disconnection within networks, probably depends on correct forms of rerouting ("functional plasticity," see Fig.1). Plasticity

is functional if it compensates for a disconnection between way-stations (e.g., between globus pallidus and thalamus). "Dysfunctional plasticity" (e.g., from caudate to thalamus) may reduce the efficiency of the repair or even negate its effects if the new route bypasses critical parts of the network (e.g, globus pallidus).

FUNDAMENTAL COGNITIVE AND BEHAVIORAL DEFICITS IN AUTISM

There have been a number of attempts to tease apart the cognitive and behavioral deficits that occur in autism, and to hopefully



identify some as more fundamental than others (for reviews, see Bailey, Phillips, & Rutter, 1996; Happe & Frith, 1996; Rapin 1997; Rumsey, 1996; and Litrownik & McInnis, 1982). A recent example has been attention to the lack of a *theory of mind* in autism. Theory of mind was the term used by Premak & Woodruff (1978) to describe an individual's understanding of the motives, knowledge, and beliefs of others. Frith, Baron-Cohen, and others (Baron-Cohen, 1995; Baron-Cohen & Swettenham, 1997; Frith & Happe, 1994) have noted that autistic individuals do not seem to have such understanding, nor are they able to develop it. Consequently, these authors have posited that a deficit in the primitive functions that form the basis for having a theory of mind could be a major cause of the difficulties in autism. However, just what constitutes a theory of mind, who has it, and whether it is truly impaired in autism has been debated (see, for example, Povinelli & Preuss, 1995).

A different, perhaps more fundamental deficit should be entertained as being present in many persons with autism, particularly if they are low-functioning: a deficit in the ability to selectively manipulate sensory representations, concepts, and thoughts. This manipulatory deficit would be independent of the sensory representations, concepts, and thoughts themselves (although these may also be deficient). In basic terms, this is a problem with the *ability to imagine*. However, it is not a deficit in simple visual imagery; there is self-reported evidence that high-functioning persons with autism not only have visual imaginations but rely upon them (Grandin, 1997). Instead, what is referred to here is the ability to select elements of mental states and manipulate them. Normally, humans are able to focus on different aspects of an object or experience, and even seem to be able to break these aspects

away from the original experience and manipulate them separately. A person can see a red cup and separate out its redness from its shape. Persons with autism, however, are notorious for not being able to do this. They are notorious for context-dependence and for apparently focusing on the "wrong" features of everyday objects.

There is some evidence that, in normal individuals, this ability to select features from otherwise unitary representations is dependent upon the prefrontal cortex (Thompson-Schill, Esposito, Aguirre, & Farrah, 1997). A deficit in such functions would certainly fit with many of the other noted behavioral characteristics of persons with autism: their rigidity, repetitive behavior, and perservation; their lack of symbolic play; and, more elaborately, a theory of mind. Deacon (1997) and others have suggested that this type of mental manipulation, which is essentially symbolic, is one of the important mental prerequisites of humanness.

Within the subgroups of autism, much still needs to be explained. Each of the subgroups (described in Zimmerman & Gordon, 2000) is known to be associated with at least two paradoxes. One is that autistic individuals often have disproportionate mental abilities and skills, in addition to their obvious disabilities. The other paradox is that, despite the clear cognitive and behavioral abnormalities in each of the autistic categories, the underlying neural pathology still seems to resist a consistent description. Going back and reclassifying the pathology of autism into clinical subcategories does not yet result in a more coherent picture. According to published studies, even within these clinical subcategories, reported abnormalities may be present in some individuals and absent (or different) in others. The inability to find beneficial effects of any categorization scheme may simply reflect how conflated these categories

have been in reported studies, and in the impossibility of reconstructing them from the published accounts. It is also very possible that some heterogeneity—in mental functions as well as in neuropathology—will prove to be a fundamental characteristic of each category of autism.

Behavioral Heterogeneity

One of the most striking features of autism is that that it is often accompanied by relative strengths in some areas of cognition, in addition to disabilities in others (Happé & Frith, 1996; O'Connor & Hermelin, 1989). Such patterns are well known in developmental disorders. In Williams syndrome, speech, surface language abilities, and (at times) musical ability, are typically far superior to visual-spatial abilities and to general cognitive abilities (Capirci, Sabbadini & Volterra, 1996; Tager-Flusberg, Boshart, & Baron-Cohen, 1998). Many of the developmental syndromes of mental retardation have relative preservation of visual-perceptual ability (Pulsifer, 1996). However, supranormal islands of ability are much rarer in other conditions compared to autism spectrum disorders (Happé & Frith, 1996). It has been claimed that 10% of the autistic population has “special abilities” (Rimland & Fein, 1988). The supranormal skills that have been described in both autistics and in individuals with other diagnoses include lightning calculation, calendar skills, list learning (Mottron, Belleville, Stip, & Morasse, 1998), visual memory, hyperlexia, puzzle construction, drawing ability, musical memory, and playing by ear and improvisation. (For more complete lists, see Happé & Frith, 1996; O'Connor & Hermelin, 1989.) Regardless of the exact proportion having such abilities, the overabundance of such skills demands some explanation and might even shed some light on the nature and neurobiology

of autism itself, as Frith (1989), O'Connor (1989), and others have suggested.

Not all of the apparently superior skills that have been reported are difficult to explain. Restricted attentional focus, repetitiveness, and the lack of competing thoughts or abilities (Frith, 1989) can certainly account for many apparent abilities. A recent study of atypical memory abilities in one individual (Mottron et al., 1998) is perhaps an example of how superior performance in one area may be accounted for, in some instances, by actual cognitive deficiencies in other areas.

However, there are other examples of apparently superior ability that seem to arise spontaneously (e.g., Selfe, 1977) and do not seem to be easily explained by the absence of normal mental impediments. These often seem to involve implicit learning of rules and patterns (Hermelin & O'Connor, 1986). They also often seem to be remarkably circumscribed. An individual who can do lightning calculations of dates may not even be able to multiply numbers (Happé & Frith, 1996). It may not be unreasonable to ask that any unified account of the neural basis for autism account for these abilities as well as autism's documented disabilities.

NEURAL NETWORK THEORIES

It may be possible to unify both the behavioral heterogeneity—the abnormalities and the supernormalities—as well as the possible neural heterogeneity. To do so requires a digression into neural network theories. (It should be noted that Cohen 1994 raised many of the same hypotheses proposed here.) Neural network theories of cognitive processes posit that many mental operations are carried out through successive sets (layers) of neuronal processing elements. (For a brief overview, see Gordon, 1997.) With the proper

input and training criteria, and the proper learning of rules, such networks have proven to be extremely adept at embodying rules and patterns that are implicit in the data presented to them. However, the accuracy of this extraction is very dependent upon the number of processing elements in the active learning layer (Baum & Hausler, 1989). If there are too few elements, then the network does not learn with very good accuracy: it, in fact, tends to over-generalize. If there are too many elements, then the network learns each specific situation presented to it and doesn't generalize enough. If some number of working elements leads to adequate performance, a somewhat greater number can result in truly superior performance in learning implicit rules and patterns, as long as it avoids becoming too specific.

This observation might be tied in to normal development, and to the abnormal development(s) that occur in autism, in the following way: the normal development of higher cerebral functions in a child's cortex appears to be driven by at least two major influences. One is predetermined connections: the other is activity and use. It has often been noted that the number of genes coding for the brain and neural tissue (~50,000) are insufficient to specify all the connections of the mature brain. Thus, the development of these connections must be guided in part by experience. Edelman (1987) and Intrator and Edelman (1997) have suggested that whether an uncommitted area develops connections with one region or another is based on the outcome of a competition for use. The developing child's brain normally has several primary sensory inputs, including vision, audition, and touch. These inputs are hardwired and fairly compelling. Such sensory inputs will do all they can to recruit whatever upstream neuronal processing resources are not yet committed.

Normally, the multiple influences on a child lead to a balance of forces, with the normal balance of lower and higher processing abilities (and neuroanatomic maps) as a result. The amount of neural tissue that is devoted to each higher function therefore represents a tradeoff between several forces: an attempt to optimize processing, the practical limits on optimization (because of lack of enough experience and training time), and competition with other functions for those same neuronal processing elements.

What if a developing brain had all those same forces at work, but for some reason some processing systems were impaired or delayed in their development? What if the systems in question were those involved in speech perception and speech production? Specific genetic deficits in speech production have been tentatively identified. It is conceivable that there are other deficits or combinations of deficits with more widespread effects on both speech production and speech perception. If the systems related to speech perception and speech production were developmentally impaired, then many higher abilities dependent upon appropriate auditory input and output would never develop properly. Whatever cerebral tissue would have been devoted to those higher functions would then be free to be incorporated into other processes (assuming the tissue itself was not too badly affected by the same defects). If vision were intact, then visual-related abilities would be expected to appropriate the extra cerebral tissue. The result would be a child's brain that was not capable of all of the normal functions of a child, but that was capable of performing some functions superlatively well. The brain would not be capable of those abilities that are related to speech and language capability, such as a long-term component of working memory (the part normally dependent upon an articulatory loop), and perhaps even such

higher functions as the “inner voice” aspects of consciousness. It would, however, be extraordinarily good at wordless visual perception and analysis. Neuropathologically, such a brain might have only a few, apparently nonspecific, abnormalities. It would not have to have fewer neurons than normal. Autistic brains are, if anything, average or larger-than-average in size (Courchesne, Muller & Saitoh, 1999; Lainhart et al., 1997). It might be possible to detect additional territory devoted to visual-related functions, but perhaps not with current behavioral tasks and instrumentation. Autism may therefore represent disorders of activity-dependent plasticity during brain development that occur at several different levels: gene, synapse, neuron, network, and neuronal group.

Hypothesis of Activity-Dependent Plasticity

In broader outline, the hypothesis is this: Either because of genetics or external influences, several regions or neuronal networks of the developing brain are damaged or delayed in their development. Regions involved in social connection and those involved in speech and language seem to be particularly susceptible. (It is not too speculative to imagine that they have a functional linkage and perhaps, therefore, a genetic one as well.) There are two consequences of this primary pathology. Functions that require these inputs cannot develop fully. Functions that were not dependent upon these impaired routes can develop normally, and might well develop supranormally. They would develop supranormally if these functions were normally kept constrained by a competition for neural resources from the functions that were now impaired (with the competition being

either in functional space or perhaps just through simple anatomic proximity).

This hypothesis has several testable consequences. There will be *forme frustes* of autistic disorder—in speech and language and in socialization—representing less extreme forms of the autistic pathology. These types of deficits should be familial. The domino effect on functions should be predictable after research establishes a better understanding of what functions depend upon other functions, in both development and in operation. Finally, it should be possible to identify some *in vivo* correlates of the extra neural tissue that has been adopted for processing (e.g., vision) in these individuals.

This hypothesis does not explain the primary cause or causes of the deficits. It would, however, help to explain why persons with autism tend to have the patterns of disabilities and abilities that they do, and why their neuropathology (in the broadest sense) has been so variable from individual to individual. It might also suggest ways in which functional retraining can try to ameliorate some of their disabilities or take advantage of their particular strengths.

CONCLUSION

The next stages of investigation of neural mechanisms in autism spectrum disorders should first focus on the selection of subjects and clinical definition of subsets. Although well-studied animal models are desirable, high-functioning subjects with autism are more likely to reveal the essential abnormalities in this very “human” disorder. Multiple investigative techniques, from cellular and neurochemical to cognitive neurophysiology, and quantitative and functional neuroimaging, will help to define the neural networks that contribute to autism. ■

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