The Neurodevelopment of Autism: 
Recent Advances

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Introduction

During the past several decades researchers have been trying to show that people with autism have definitive brain damage. However, despite the use of more sophisticated brain scanning and imaging methods that have recently become available, there is no evidence of "brain damage" per se. As Bauman (1993), who has conducted some of the most thorough and detailed neuroanatomical examination of human brains from autopsy material has stated "there is no evidence of 'brain damage' in the usual sense." Earlier Tsai (1989) had come to a similar conclusion when he reported that "results from neuropathological and brain imaging studies strongly suggest that the cerebral defect in autism is microscopic or functional, without gross neuroanatomical pathology."

Bachevalier (1994) in a very comprehensive review of numerous studies looking for cortical malformations, concluded that, "a direct role in the pathogenesis of autism seems unlikely" because no malformations confined to any specific area of the cortex could be found and they were not even present in most subjects. Yet, despite these convincing conclusions, researchers continue to look for the "holes" in the brain. Unfortunately, this kind of zealous search for neuroanatomic defects predisposes most of us to think that all people with autism must somehow be deficient because, after all, they must have damaged brains and it will only be a matter of time until technological advances produce higher resolution techniques that might find the "holes" or other anomalies in their brains.

This article argues that it is time to take a different approach and that there is much more hope for remediating the autistic brain than once thought because of recent neuroscientific findings. Fortunately, recent discoveries in the way the brain develops, from the moment of conception and during the early years, provide greater insight into the construction timetable of the human brain and the capacities and limitations imposed on behavioral and other interventions. Rather than being seen as a static event, it is important to keep in mind that the development of the brain is a dynamic process that is constantly evolving and changing in concert with the environment in which the child is placed. The limiting factors are both the biological structure of the brain as well as the environment. Limiting either one will compromise human potential. Conversely, enriching both will enhance the road to developing an individual's full potential. This paper explores the manner in which the brain develops from the point of conception, key developmental events that may be crucial to understanding the behavior of a child with autism, and the need to provide the most conducive environment to enrich brain functioning early in life and maximize the functional capacity of the individual with autism.

Neurodevelopmental Process

The earlier analysis of data typically divided gestation somewhat arbitrarily into three periods or trimesters, with little consideration of brain development. Schull and colleagues (Schull and Otake, 1986; Otake, Schull and Yoshimaru, 1991), have shown that, based on what happens from a neurodevelopmental perspective, it makes far greater sense to divide the gestational period into four
"critical" periods. It can be seen from Table 1 that the four critical periods correspond to major events of brain neuronal development.

<table>
<thead>
<tr>
<th>Trimester Timetable</th>
<th>Neurodevelopmental Timetable</th>
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<tr>
<td>0 - 12 weeks</td>
<td>Neuronal Proliferation</td>
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<td>0 - 7 weeks</td>
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<td>13 - 25 weeks</td>
<td>Migration of Neurons</td>
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<td>8 - 15 weeks</td>
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<td>25 - 39 weeks</td>
<td>Differentiation of Neurons</td>
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<td>Continued Differentiation</td>
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<td>26 - 39 weeks</td>
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Table 1: A comparison of the trimester periods of gestation and a timetable formulated on the basis of major neuronal stages of growth and development.

During the first few weeks of gestation neural cells begin to proliferate at an exponential rate, peaking at a rate of approximately two hundred and fifty thousand per minute. At around the eighth week, neurons begin to migrate from the deepest layer of the brain out towards the periphery or cortex. Each neuron has a specific address and it has to reach that final destination if it is to perform the functions for which it was designed. As Schull (Schull and Otake, 1986) has pointed out, cells have to be in the right place to perform their correct functions. They cannot perform correct functions if they are not in the proper place at the right time. In this regard, brain functioning (and consequently early behavior) is critically dependent upon the position of neurons in the brain or the structural composition of neuronal networks (brain matter). Therefore, if the normal sequence of development is disrupted in any way, the consequences can be far-reaching. This is especially the case when neural migration is disrupted. Schull and others (Clarren, 1990; Streissguth, Barr and Martin, 1984) have shown that radiation or alcohol ingestion during the eighth to sixteenth week of gestation produces mental retardation in over eighty per cent of cases. This is, therefore, a critical period of development that will have lifelong consequences on behavior that are irreversible.

After about the fifteenth week of gestation, when most of the neural brain matter is already laid down, the neural cells begin to differentiate or branch out. At around thirty weeks the neurons in the cerebellum begin to connect with other areas. The cerebellum is critically important for coordinating many aspects of brain processing. It is a veritable relay station, connecting with all other important brain regions. Thirty weeks is a crucial period for the all important Purkinje cells to complete their intricate connections with other neural fibers. Purkinje cells in the cerebellum are very large neurons that form extensive parallel networks with other neurons from many regions of the brain, thereby allowing coordination of functions vital to the survival of the newborn. Although developing later in the gestational timetable, the cerebellum is normally fully formed at birth, even though not yet entirely mature. Basically, the neurons begin to connect with others through further development and maturation. This period of differentiation continues as the process of myelinization (insulation of nerve fibers) begins and continues until birth and well after, into the early childhood years.
From the point of conception until birth, neural brain cells migrate and develop at different times, move to different sites, and do so at varying but quite rapid rates. It is important to keep in mind that many processes are underway during gestation -- neural cells proliferate and migrate, then differentiate, dendrites (the end branches of neural cells) and axons (the stem of neural cells) grow at varying rates, synapses (the gaps between neural cells which contain transmitter substances) form and some are lost, and myelin (a white fatty tissue) insulates axons and speeds transmission of signals. After birth the process continues, although at a relatively slower pace during the first two years of life, and then slows down in pace in the years to come and finally reaches a plateau around fifteen years. Any invasive event that disrupts this course of development will have more profound effects if it occurs earlier in the developmental timetable, because obviously more neural tissue will be involved in such a case and the consequences on behavior will be more profound.

**Neurodevelopmental Course of Autism**

Most recent neurobiological data suggests that autism is caused by late disruption of the Central Nervous System (CNS) just prior to birth, perinatally, or postnatally (Bachevalier, 1994; Kemper and Baumann, 1993). When viewed from a neurodevelopmental perspective, this is very encouraging because it means that most all of the neurons have already been established and therefore very little neural tissue would be damaged or affected. It follows from what was said previously about the timing of a disruptive event that later disruption will produce less neural tissue involvement, if any at all. This certainly corroborates the findings by Tsai (1989) and Kemper and Bauman (1993) that there is no gross neuranoatomic involvement in autism. It may also offer much greater hope for reversing the behavioral disturbances that occur with the syndrome of autism.

Most interestingly, data from some of the most carefully conducted studies (Kemper and Baumann, 1993; Coleman, Romano, Lapham and Simon, 1985) suggest that the cortex or outer layer of the brain in autism is intact and has no structural abnormalities. Their investigations suggest that any disruption in the developing brain of someone with autism occurs before the thirty week period of gestation and specifically disrupts connections in the midbrain and brainstem areas. This is a period of time when neurons are primarily differentiating and making connections with each other from one area of the brain to another. Such interconnections are vital to the successful integration of information that accompanies typical brain information processing and adaptive behavior. Kemper and Bauman's (1993) studies indicate that the primary areas of abnormality in autism occur in two areas, the limbic system and the cerebellum and its circuits.

The limbic system plays a significant role in various aspects of emotion, memory and learning, and motivation. It includes multiple areas of the brain - the hippocampus, amygdala, mammillary bodies, anterior cingulate gyrus and nuclei of the septum. Kemper and Bauman's (1993) studies indicate that the neural cells of the limbic system in autism are small in size and more densely packed per unit volume as compared with age and sex-matched controls. Such a picture is consistent with a chronologically younger brain where the limbic system is curtailed in its development. The fact that the brain cells are so tightly packed and small suggests that the normal atrophy of some of the cells was disrupted. In any event, the consequence is abnormal information processing at this level of brain functioning.

The second major area of abnormality found by Kemper and Bauman was in the cerebellum and its many circuits and interconnections. Basically what they found was a substantial loss of Purkinje cells throughout the cerebellum, especially in the posterior regions. The loss of Purkinje cells helps establish the timing of the abnormalities. During gestation, climbing fibers start out from the olivary nucleus,
located in the brainstem, and migrate to connect posteriorly with Purkinje cells. Research studies in humans suggest that these connections occur at thirty weeks of gestation. Also, once the connections are made, the system becomes one single unit (olivary nucleus, climbing fibers and Purkinje cells). Should anything happen to the Purkinje cells after the connections have been made, the entire system degenerates and atrophies. However, in the brains of people with autism Kemper and Bauman found that, even though there was a major loss of Purkinje cells, the olivary nuclei were preserved. This suggests that whatever happened to the Purkinje cells had to have happened just prior to thirty weeks of gestation. Furthermore, they also found that many of the neurons concentrated in the deep nuclei of the cerebellum, those responsible for input and output of information and communication with other portions of the brain, were abnormal. In the younger cases, the neurons appeared normal but were abnormally large ("hypertrophied") whereas in their older cases the same neurons were reduced in size in every case and there was evidence of cell loss. They hypothesized that, because of the loss of Purkinje cells, the normal circuit (i.e. olivary nucleus, connecting fibers and Purkinje cells) was not established and the autistic person had to rely on to the more primitive circuit as the dominant means of neuronal communication. Furthermore, they postulate that because the more primitive fetal circuit was not designed for adult life, they become enlarged (hypertrophied) in response to extended demand and may eventually "burn out" and die. This would especially be the case if there was no attempt to modulate the stimuli reaching the young autistic brain and cause it to become overtaxed and unable to handle external demands. On the other hand, a program designed to deliver stimuli or information in a carefully modulated manner would give the autistic brain a better opportunity to process the information more adaptively without the overload. It would give the developing brain an opportunity to establish more normal circuitry through the brain structure - brain function inter-relationship. It is well known that brain structure initiates brain function, but that structures only develop appropriately if they are in turn stimulated by external environmental events (Hudspeth and Pribram, 1992). The structure and function cycle is crucial for the growth and maturation of the brain and, consequently, adaptive behavior. Obviously any program designed to enhance the more normal growth and development of the brain increases the probability for more normative brain-behavior functioning. How much can be done to establish normal brain development and functioning in someone with autism, from a purely neuroscientific viewpoint, still remains to be seen. More research is obviously needed in this area to definitively answer this question. Nevertheless, the findings reviewed in this paper suggest that much can be gained if the appropriate program is used with autistic children, starting at a very early age and applying the correct technique intensively for a duration of several years.

**Subclassification of Autism**

A review of the most carefully controlled neuroscientific studies (Bachevalier, 1994) using various methods such as autopsy material, brain scanning and imaging (MRI, CAT, PET, SPECT, rCBF) suggest that it may be helpful to divide autism into two distinct subclasses: Type1, where there are distinct neurologic signs and varying ranges of mental retardation (encompassing approximately 60-70% of the autistic population); Type 2, where the CNS is anatomically intact and there is no mental retardation (encompassing approximately 30-40% of the autistic population). Obviously a continuum from severe functioning deficits to very minor exists in the autism population. DeLong (DeLong and Nohria, 1994) has appropriately described this phenomenon as the "spectrum" of disorders in autism. The two sub-types should be seen as fitting into such a spectrum or continuum.

It makes greater sense to subclassify autism in the above manner when the neurodevelopmental evidence is taken into consideration. For example, we know from the earlier discussion about critical periods, particularly during 8-16 weeks of gestation, that mental retardation is most likely to occur if any...
event interferes with the process of neuronal migration. This earlier onset disruption of the developing fetus, regardless of the cause, would produce more severe consequences. This type of disruption would affect many brain areas and have definite abnormalities such as those seen by Kemper and Bauman (1993). Cells in the limbic system (amygdala, hippocampus, cingulate, septum) would most likely be affected. The development of the Purkinje cells and deep cerebellar nuclei would also undoubtedly be affected. In this case, many neural circuits would not be properly formed and brain functioning would therefore be compromised later in life. The blend with mental retardation would make it difficult to reverse the brain functioning difficulties found with such people. Level of improvement would obviously be influenced to a very large extent by the degree of brain impairment.

In the second type of autism proposed, any disruptive event would have to occur later in the gestational timetable and would, therefore, hardly disrupt brain development at all. In this case there would be no anatomical abnormalities as the neural structures would be fully formed. Therefore, we would expect to find very subtle anatomical signs, if any, as has been reported by Kemper and Bauman (1993) and Tsai (1983). Most likely the major problem related to brain functioning would be dysfunction of the neurotransmitter system where the chemical substances responsible for conducting nerve impulses across synapses would be affected. Such a situation is much easier to reverse or correct, either through pharmacological therapy, by activating the correct pathways in the young brain that produce normative brain development, or both.

**Predicting Successful Outcomes**

The neurodevelopmental findings discussed previously, when combined with the growing clinical and experimental evidence on the memory systems necessary for learning, can help us understand the most effective ways to teach youngsters with autism and produce more successful outcomes. For example, the work of Mishkin and others (Mishkin and Appenzeller, 1987; Zola-Morgan and Squire, 1993; Bachevalier, 1990) has shown that there are basically two types of memory systems which underlie successful learning. The first has been referred to as "habit, rote, or procedural" memory. This system develops early and becomes functional during the first months of life in humans. It is the kind of memory we use for skill learning and is acquired by repeated presentation of the same stimulus until the task is correctly stored and accessed in memory and thereby learned. The striatum and neocortex of the cerebral hemispheres are the areas which mediate this kind of memory. It will be recalled that both of these brain structures have been found to be anatomically intact and normal in the brains of children with autism.

The second type of memory evident from the work of Mishkin and his colleagues has been termed the "representational, associative, or cognitive" system, which is anatomically distinct from the "habit or procedural" type mentioned previously. Most importantly though, Mishkin states that the "representational" system coordinates all of the sensory modalities, including the processing of experiences and events, and the generalization of such information which leads to higher-order cognition and learning. This "representational" system depends on the integrity of the limbic system, especially the amygdala and hippocampus and areas connected to them. Any disruption to these connections or limbic areas would interfere with the acquisition and meaning of information obtained from the continual presentation of novel stimuli typical in the daily life of a developing infant and child. There is little doubt that disturbances in the CNS which would disrupt the "representational" system would lead to disorganized cognition, problems with modulation of sensory events, inappropriate social interaction and abnormal language development. These are the features so typical of autism.
From what has been discussed so far in this paper, conclusions can be drawn as follows: a). Children with autism, particularly those that fall into the Type 2 classification (probably also a large number of the Type 1) have intact brain cortices and, therefore, their habit, rote, or procedural memory systems should be intact. They should be fully capable of acquiring skills through repeated presentation of stimuli until tasks are properly learned. They will appear to be quite normal during their first few years of life and then show difficulty acquiring language and social skills because of disorders in their limbic system and cerebellum disrupting "representational" memory functions. However, due to the nature of the late onset of disturbances in brain development, they should be prime candidates for recovery if given the appropriate treatment early in life (certainly starting at around two years of age or soon thereafter) so that their limbic and cerebellar circuits can be activated and they can utilize their associative or representational learning systems. This would allow them to form basic cause-effect relationships, associations and generalizations so crucial to adaptive behavior functioning. b). Children with autism falling into the Type 1 class who most likely had earlier onset disruption of a critical period of brain development (most likely starting early in gestation during the 8-16 week period) and therefore different levels of mental retardation complicating their autism, would have less probability for full recovery. However, if their cortical brain areas are intact, they too would be quite normal in their first two years of development and they would have normal rote or habit learning. They should, therefore, acquire early rote learning skills easily, provided they are placed in an environment ideally suited to maximize such learning through repeated presentations of stimuli. Once they acquired the necessary rote learning, which is a prerequisite to the higher-order or associative learning system, they could then be taught to use the latter, depending on the integrity of their limbic circuits. The best way to determine how much these children would be constrained in their learning would be by screening them comprehensively with neurodiagnostic techniques. Those children discovered to be neuroanatomically "intact" would undoubtedly experience the most success following intensive teaching and training. Those with neurological involvement would learn skills to a lesser extent, yet still profit greatly from intensive early intervention.

What follows, therefore, from the above discussion is the critical need to carefully screen children suspected of having autism, at the earliest possible moment in life, using thorough neurodiagnostic methods. This will assist in predicting learning potential and recovery to a great extent. Also, just as important, is the need for early intervention or therapy which will allow the youngster with autism to maximize rote learning capabilities and then move on to higher-order, associative, learning. Since the ability to transfer skills from the rote to the associative stages is critically dependent upon the interaction of brain maturation and stimulation from the outside environment, it is crucial that the correct teaching strategies be started early, that they be presented consistently and repeatedly over most of the time the child is awake and functioning, and for several years in duration. We know from neuroscientific evidence that neuronal networks develop and mature very slowly over time in humans. Any lasting changes to such a slow developing system takes many years (Hudspeth and Pribram, 1992). Given what we know of brain development and what has been discussed in this paper, it is hard to conceive of any techniques of teaching or remediation that will be effective with the autistic child unless they meet these conditions. This kind of knowledge certainly argues very strongly against any short, or brief, therapies being capable of establishing long-lasting changes in brain functioning and behavior.

Fortunately, several recent studies (Lovaas, 1987; Perry, Cohen and DeCarlo, 1995; Wetherby, Koegel and Mendel, 1981; Luce, Niemann, Wright, and Dyer, 1995) support the notion that early, intensive therapy of several years duration are most effective in treating autism. These methods not only meet the criteria of early intervention and intensity over time but also start out by teaching rote learning skills in an ideal format of repeated presentation, at the correct pace, along with numerous contingencies of
optimal reinforcement. Following the acquisition of basic rote skills, such programs then move on to the higher-order associative skills which allow generalization and the development of more adaptive behaviors necessary for independent daily functioning. These studies, in effect, follow the ideal course of brain development and employ the best principles of brain maturation and development. Little wonder, then, that they can achieve such good outcomes and report various levels of recovery from earlier autistic behaviors.

From what has been presented in this paper, it can be argued that autism should be reversible, possibly in at least 40 to 50% of cases, provided they are properly identified, carefully screened neurologically, and provided early intervention that is intensive on a daily basis and lasts several years. This is the encouraging news. However, it also raises a dilemma because we know from brain development that there is a narrow window of opportunity to achieve optimal results. Waiting until the child is five or six years old may be too late because the brain may already have passed the stage of plasticity which would allow it to benefit from any remedial technique, no matter how intensive. Any child with autism who is not given early intervention of an intensive nature may, therefore, be deprived of an opportunity to change later in life. This may lead to permanent disabilities that will continue to exact more costly emotional and economic costs on the individual, his family, and society. It also raises the issue of neglect for those cases that never get appropriate therapy. Such issues will undoubtedly keep debate alive in this area for years to come. Nevertheless, it is hoped that the recent findings in the neurosciences that have been reviewed in this paper and offer so much hope for improvement, will lead to more urgently needed research and to a greater understanding of autism and how best to maximize functioning for people born with this syndrome.

References


