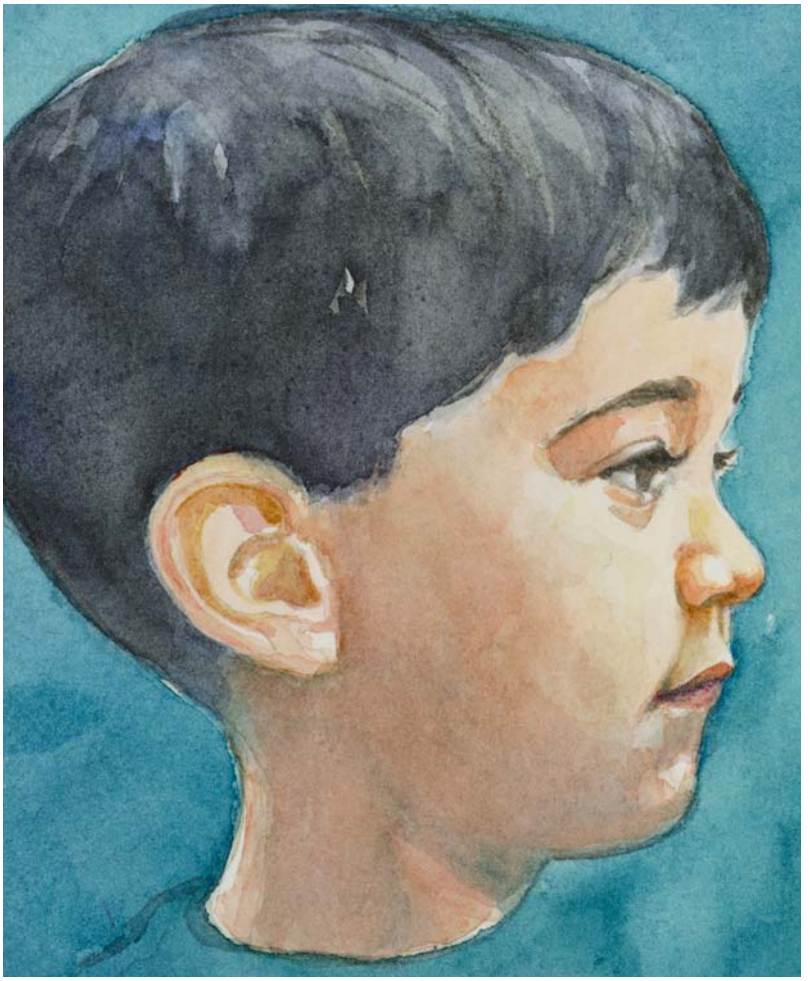

Bringing the Brain of the Child with Autism Back on Track

What if we could identify some common process that goes awry in the developing brain of a child and leads to errors in wiring that cause the devastating symptoms of autism? What if, understanding that malfunction, we could intervene with drugs and behavioral therapies that don't just mask symptoms but actually bring the child's brain development back on course? Wayne State University professor of pediatrics and radiology Diane C. Chugani, Ph.D., describes new insights achieved through molecular neuroimaging that may —repeat, may—change how we understand and treat autism.

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by Diane C. Chugani, Ph.D., and Kayt Sukel

Bringing the Brain of the Child with Autism Back on Track

Many parents of autistic children speak about their child in terms of "before" and "after." They reminisce about their child's babyhood, full of play, smiles, and the early developmental milestones so easily reached. But then, they say, seemingly overnight, things dramatically changed.

The lively sounds that so closely resembled speech never quite evolved into actual words; instead they regressed into grunts and nonsense noises. The child who was once content to be held in Mama's arms now recoiled from her touch, and any small change in routine could result in inconsolable screams. Many say that it was almost as if their child had suddenly and mysteriously changed into an entirely different person.

Parents of autistic children usually witness this profound and often abrupt metamorphosis in their son's or daughter's development at some point between the one- and two-year mark. They wonder if perhaps the

disorder could have been avoided had they caught it earlier or done something—anything—differently during that critical period. So far, the answer has always been no. New research, however, may change that answer.

THE POTENTIAL FOR TREATMENT, NOT MANAGEMENT

In this article we will explain why we believe that discoveries made using molecular neuroimaging offer the promise of a new approach to treating autism during critical periods of brain development. In the past two decades, scientists have made substantial advances in understanding autism and how it affects brain development and behavior. Research in genetics, functional neuroimaging, and cognitive neuroscience has provided helpful knowledge about potential causes of autism, as well as the range of behavioral effects. Although these studies have been invaluable in understanding more about the disorder, it is research at a more basic level that may provide the start for a new and unique method of treatment.

The ability to examine the brain of living subjects at such a fine level of detail allows greater understanding of the processes that underlie normal brain function and presents an opportunity to see how we might intervene if those processes are not functioning correctly.

What is called molecular neuroimaging allows researchers to measure biochemical changes in the brains of living humans. One powerful technique, positron emission tomography (PET), measures the location of a radioactive tracer as it travels through the body, including the brain. By selecting the right biochemical from the more than 1,400 that have been radioactively tagged, researchers can measure such processes as the metabolism of glucose, how proteins are synthesized in different areas of the body, blood flow, and how neurotransmitters bind to neural receptors. For example, by using PET to track a radioactive tracer that is converted in the body to a specific brain chemical such as the neurotransmitter serotonin, researchers are now able to examine how much of that neurotransmitter is made in a person's brain. The ability to examine the brain of living subjects at such a fine level of detail allows greater understanding of the processes that underlie normal brain function and presents an opportunity to see how we might intervene if those processes are not functioning correctly.

Recent research using molecular neuroimaging has provided critical information about how the processes in the developing brain of an autistic child differ from those in the brain of a child without the disorder.

Previously, very little was known about the biochemistry of the developing brain, but structural and molecular neuroimaging studies have provided us with significant clues by showing dramatic differences in brain growth and levels of the neurotransmitter serotonin in children with autism. Other research has also provided insights into the autistic brain by showing differences in the organization of neurons in the cortex and decreased numbers of certain types of cells that make up the cerebellum.[1,2] Careful study of the details of these differences in brain development may provide a basis for designing new drug treatments for autism, treatments that would not manage behavior, as is the case now, but rather would work directly to bring the brain development of the autistic child closer to the normal range.

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MULTIPLE CAUSES, MULTIPLE EFFECTS

One of the biggest problems in succinctly defining autism—and consequently in recommending treatment—is that the disorder exhibits such a broad array of characteristics. Autism is defined by the presence of multiple communication, social, and stereotyped behavioral difficulties that begin before three years of age. Furthermore, autistic behaviors vary according to both developmental level and chronological age. Problems in communication can range from no language at all to more-subtle language difficulties, such as delay in word acquisition or pronoun reversal. Stereotyped behaviors such as hand flapping and spinning are typical of young children with the disorder, whereas older, high functioning people with autism often evidence a need for sameness or a focused interest in a particular activity or topic. In addition, many autistic children suffer from a host of other complaints, such as extreme reactions to sensory stimuli that would not bother most people and aggressive or self-injurious behavior.

Underlying this spectrum of behaviors are undoubtedly multiple causes, only a small fraction of which have thus far been identified. Recent

1. Casanova MF, Buxhoeveden D, Gomez J. (2003). Disruption in the inhibitory architecture of the cell minicolumn: implications for autism. *Neuroscientist* 9, 496-507.

2. Bauman ML, Kemper TL (1994). Neuroanatomic observations of the brain in autism. In: Bauman ML, Kemper TL (eds.) *The Neurobiology of Autism* Johns Hopkins Press, Baltimore, pp. 119-141

research has shown that autism may be a component of several genetic disorders, including fragile X syndrome, phenylketonuria, tuberous sclerosis complex, and Rett syndrome. But even in cases where genes are identical (such as when identical twins have the disorder), the symptoms may manifest themselves in profoundly different ways—for example, with one twin showing delay in language acquisition while the other struggles with a sensory impairment.

Despite the diverse causes that may underlie autistic behavior, we cannot exclude the possibility of a few common neurochemical features. One of these may involve the synthesis of serotonin, a neurotransmitter critical to normal development in the brain.

Brain development involves a series of biochemical "programs" that are turned on and then turned off as the child's body builds itself. Just as the building of a house is accomplished through a series of steps—laying the foundation, erecting the beams, adding the bricks and mortar, and so on—the brain begins with the birth of neurons (neurogenesis), the formation of the connections between those neurons (synapses), and the refinement of electrochemical networks as children interact with the environment through their five senses. As a result, not only are children's brains different from those of adults, but the brains of infants are markedly different from those of toddlers, and those of toddlers are very different from those of older children and adolescents. Moreover, the programs can go awry at any point.

Developmental disorders, including autism, result from errors in the normal sequence and duration of the programs of brain development.

Developmental disorders, including autism, result from errors in the normal sequence and duration of the programs of brain development. These changes may result from a variety of genetic or environmental causes, but the disorder is still characterized by those deviations. Information about the deviations provides us an opportunity to seek a way to intervene in the developmental process at some critical point and help it get back on track.

THE BENEFITS AND RISKS OF PET

Using PET, researchers have studied the biochemical changes crucial to normal development in the brains of infants and children at various ages. In the majority of the PET studies published thus far, the subjects were children who had a variety of neurological or neurodevelopmental

conditions, with comparisons being made among groups of children with different disorders. The optimal design for such studies, however, would be to compare experimental results from a group with a disorder —such as autism—with results from an age-matched group of children who do not have any neurological impairment.

PET imaging studies do carry some risks, among them possible negative effects from radiopharmaceuticals, the use of sedation, and exposure to ionizing radiation. Thus, while the best comparison group for research would be children without the disorder, some people hold that using the radioactive dye necessary for PET scanning in normal children is unethical. However, what is required for PET scanning is a single dose of the radiopharmaceutical in tracer quantities, which would be unlikely to result in any adverse pharmacological effects. In fact, you are more likely to find a greater number of toxins in a glass of tap water as typical doses are lower than quantities of toxins legally present in our drinking water. Even in a case where multiple scans might be necessary, PET scanning would still involve minimal risk to the subject. The average lifetime risk of dying from cancer is 23.66 percent for men and 19.99 percent for women, so the additional lifetime cancer mortality risk of 0.0005 from the radioactive exposure during a PET scan seems minimal, hardly more than that from events of daily life, such as getting sunburned at the beach.

Given the critical information that these studies can reveal about brain development and, of course, the profound differences in the brain at different ages, it would seem that the benefits of the procedure far outweigh the risks.

SEROTONIN IN THE AUTISTIC BRAIN

Although evidence exists for the potential involvement of several neurotransmitters in autism, research has shown consistent abnormalities involving the neurotransmitter serotonin in brain development programs.[3] We have chosen to focus on serotonin here as one particularly promising avenue for investigation.

In 1961, Richard J. Schain, M.D., and Daniel X. Freedman, M.D., first reported increased blood serotonin levels in approximately one-third of people with autism, but the less sophisticated technology available at the time made it difficult to demonstrate whether the change in serotonin

3. Lam KS, Aman MG, Arnold LE. Neurochemical correlates of autistic disorder: a review of the literature. *Research in Developmental Disabilities*. 2006 May-Jun;27(3):254-89.

in the blood also signified changes in serotonin in the brain. Recently, however, using PET scanning our research team (D. Chugani) has detected differences in serotonin production between autistic and non-autistic children.[4] During early childhood, children without autism undergo a period of high brain serotonin synthesis, which then declines when they are about six years old. We hypothesize that this period of higher serotonin synthesis helps children form strong new synaptic connections in their brains. In autistic children, however, this process is disrupted. In our studies, the autistic children did not show such an age-dependent peak and decline but instead showed a consistent rate of serotonin synthesis in the brain—underproducing serotonin during the critical early years and overproducing the neurotransmitter after the age of six.

We hypothesize that this period of increased serotonin synthesis helps children form strong new synaptic connections in their brains. In autistic children... this process is disrupted.

Because of this flattened level of serotonin synthesis in autistic children, without the early critical peak that we see in children who do not have the disorder, we hypothesize that young autistic brains are not making as many, as strong, or as accurate synaptic connections between neurons.[5, 6] This could explain many of the behavioral problems observed in autistic children, including extreme reactions to sensory stimuli, for example. Some autistic children are unusually sensitive to fluorescent lightbulbs, responding hysterically to the bulbs' flickering stimuli, which might not even be noticed by a child without autism. This extreme reaction could be the result of incorrect routing of a synaptic connection during brain development, which would pair the stimulus with an uncommon reaction.

TREATMENT NOW AND TO COME

Currently, most treatments focus on managing behavior through drug or behavioral therapies. For example, Risperdal, one of the newer antipsychotic

4. Chugani DC, Muzik O, Behen ME, Rothermel RD, Lee J, Chugani HT. Developmental changes in brain serotonin synthesis capacity in autistic and non-autistic children. *Annals of Neurology* 1999; 45: 287-295.

5. Bennett-Clarke CA, Chiaia NL, Rhoades RW (1996). Thalamocortical afferents in rat transiently express high-affinity serotonin uptake sites. *Brain Research* 733, 301-306.

6. Bennett-Clarke CA, Leslie MJ, Lane RD, Rhoades RW (1994). Effect of serotonin depletion on vibrissae-related patterns in the rat's somatosensory cortex. *Journal of Neuroscience* 14, 7594-7607.

medications prescribed for schizophrenia, bipolar disorder, and agitation, has been found to be effective in treating aggression and sleep problems in autistic children. On the behavioral side, a form of therapy called applied behavior analysis focuses on teaching new skills, as well as correcting undesired habits, by breaking behaviors down into small, manageable steps and increasing a desired behavior with positive reinforcement. Unfortunately, these therapies have limited success. Moreover, they simply treat the symptoms, not the cause.

Traditionally, researchers have been reluctant to consider drug therapies for young children, in order to avoid disrupting the normal series of events in their rapidly developing brains.

Traditionally, researchers have been reluctant to consider drug therapies for young children, in order to avoid disrupting the normal series of events in their rapidly developing brains. But in the case of children with autism, that series of events does not seem to occur as it should. Therefore, a course of drug treatment during early childhood could potentially alter brain development and correct the deviation from the normal program, thus having a lasting impact on the organization of the brain and guiding its development to more closely mimic that of non-autistic children.[7,8]

Although many drugs are used to treat various diseases in children, most of them have actually been tested only in adults, not in children. And those drugs that have been tested in children have rarely been tested in very young children—even drugs routinely used to treat those children for diseases. We do need to protect children from the risks inherent in the testing and research process, but the risk of treating children with drugs that have been tested only in adults is also substantial, because the biology of the developing child is so different from that of the adult.

As we consider using drugs to treat developmental disorders such as autism, therefore, we must keep in mind that the brains of a newborn infant, an eighteen-month-old toddler, and a four-year-old have dramatic differences in the need for energy, the concentrations of neurotransmitters, and even the patterns and locations of neurotransmitter receptors.

7. Gaspar P, Cases O, Maroteaux L (2003). The developmental role of serotonin: news from mouse molecular genetics. *Nature Reviews Neuroscience* 4, 1002-1012.

8. Gross C, Zhuang X, Stark K, Ramboz S, Oosting R, Kirby L, Santarelli L, Beck S, Hen R (2002). Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. *Nature* 416, 396-400.

Because of these dynamic differences, the use of a drug that affects a receptor critical in the development of a particular brain function can actually dramatically change the course of brain development. In the past, such an effect was typically viewed as toxic—as damaging the brain, sometimes permanently. More recently, however, the possibility of using drugs during critical periods of brain development might be a way to take advantage of "windows of opportunity" to put brain development back on course.[9] Molecular neuroimaging has provided us with such a unique window by helping us understand more about how the brains of autistic children develop.

A CHALLENGE TO AUTISM RESEARCHERS

A growing body of evidence indicates that serotonin regulates several aspects of brain development, including cell division and differentiation, the growth of neurites on neurons, the creation of new synaptic connections and possible critical periods for development, and what is called activity-dependent plasticity, or when a person's interaction with the world can help the brain develop. Given this understanding of serotonin's effect on brain development and the discovery that autistic children lack adequate amounts of this neurotransmitter during early critical periods of brain development, it would seem that we have a unique opportunity to provide a drug treatment that would help regulate serotonin levels in the autistic brain and help deviating brain development to get back on course.

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Because using drugs in young children is likely to have a powerful impact on developmental processes such as synapse formation and elimination, the drugs may be particularly effective during the period of behavioral regression that typically occurs in children with autism when they are between 12 and 24 months of age—a very dynamic period for the creation of synaptic connections as well as the age period where autistic symptoms are first observed.[10] Young children have many, many

9. Andersen SL (2003). Trajectories of brain development: point of vulnerability or window of opportunity? *Neuroscience and Biobehavioral Reviews* 27, 3-18.

10. Huttenlocher PR (1979). Synaptic density in human frontal cortex—developmental changes and effects of aging. *Brain Research* 163, 195-205.

more cortical synapses in their brains than adults do. As they get older, this number decreases; some synapses that are not being used are eliminated, while those that are being used are maintained. Although scientists do not yet know the precise mechanisms responsible for this initial bounty of synaptic connections, they do know that changes in levels of neurotransmitters during developmentally critical periods can result in altered creation and maintenance of synapses.

Something as simple as a young child's interactions with the environment and other people can potentially create new and diverse synaptic connections. Spurred by these activities, synapses are created, strengthened, and stabilized.

In addition, something as simple as a young child's interactions with the environment and other people can potentially create new and diverse synaptic connections.[11] Spurred by these activities, synapses are created, strengthened, and stabilized. One process by which synapses are believed to be stabilized is called long-term potentiation.[12] During development, serotonin affects long-term potentiation in several areas of the brain, among them the somatosensory cortex, the visual cortex, and the hippocampus, as well as in the spinal cord.[13] This is particularly interesting since these parts of the brain are involved with sensory processing, an area where many autistic children have difficulties.

DESIGNING THE WHAT, WHEN, AND HOW

Using drugs that mimic the effect of serotonin in young children with autism may be beneficial in encouraging their brains to develop more normally. As we begin to design studies to develop such a treatment, however, we encounter many critical decisions: the choice of the drug, what subjects of what age to include, the duration of treatment, and whether or not the drug is paired with a corresponding behavioral intervention. Several classes of drugs specific to serotonin function could

11. Akers KG, Nakazawa M, Romeo RD, Connor JA, McEwen BS, Tang AC. Early life modulators and predictors of adult synaptic plasticity. *European Journal of Neuroscience* 2006 Jul;24(2):547-554.

12. Goodman C, Shatz C (1993). Developmental mechanisms that generate precise patterns of neuronal connectivity. *Cell* 72 Suppl 10, 77-98.

13. Edagawa Y, Saito H, Abe K (2001). Endogenous serotonin contributes to a developmental decrease in long-term potentiation in the rat visual cortex. *Journal of Neuroscience* 21, 1532-1537.

prove to be useful, among them serotonin uptake inhibitors (such as Prozac) or agonists (drugs that act like serotonin in the brain).

Although as a group young autistic children (under six years old) in whom serotonin synthesis was measured with PET showed lower serotonin synthesis than non-autistic children, the values ranged. Children with the lowest values might benefit from treatment more than children whose serotonin synthesis is only slightly lower than normal. Once again, molecular neuroimaging can help us, if we use PET scanning to identify those children who might benefit from treatment with a serotonin-like drug at an early age.

In order to determine the best time to treat an autistic child, we must consider both the normal developmental process and that child's deviation from it. Some interventions may work in autistic children only during a certain age range or during a certain period of brain development.

In order to determine the best time to treat an autistic child, we must consider both the normal developmental process and that child's deviation from it. Some interventions may work in autistic children only during a certain age range or during a certain period of brain development. In general, one would hypothesize that the earlier the intervention and the closer in time to the actual deviation in brain development, the better the outcome will be, whether this means recovery of lost function or gaining a function that might not have ever fully developed. Since serotonin synthesis has been shown to be lower in autistic children between two and six years of age, it seems that treatment should begin as soon as a child is diagnosed with autism. The earlier the disorder is diagnosed, the more effective the intervention is likely to be. This is something of a balancing act, however, since the side effects of drug treatment may be less significant at a later time.

The question of how long to treat an autistic child is similar to that of when to treat. Once again we need insight from molecular neuro-imaging into the normal course of development and the deviation from it in autism. But treatment for longer than the specific period during which a particular brain process is disturbed could be beneficial. For example, it might lengthen the critical period, providing more time for sensory interventions to affect the strength and frequency of synaptic connections. If this is the case, the length of treatment might be determined by observing when the side effects begin to surpass the perceived benefits.

Because interaction with the outside world can strengthen synaptic connections, we should also consider combining behavioral interventions with drug treatment. Since serotonin-facilitating drugs alter the formation of synapses in the somatosensory cortex, pairing them with behavioral therapies that target sensory impairments may improve the efficacy of the behavioral intervention. Conceivably, drugs could also be used to lengthen or reopen critical periods in brain development, allowing more time for acquisition of certain skills, such as those involved in language. Pairing the opening of the critical period with intensive behavioral therapies could lead to the possibility of the synaptic connections' being established outside of the normal period. For example, in an autistic child with language problems, pairing a behavioral language treatment with a drug that facilitates serotonin transmission may create the right environment to encourage the growth of stronger, more accurate synaptic connections and, therefore, help the child improve speech capability and comprehension.

DRUG INTERVENTION: A PARADIGM SHIFT

Using drugs to treat children, especially very young children, is always a matter of concern. But the greater understanding of brain development that has been gained through molecular neuroimaging suggests that pharmacological treatments may allow us to guide the brain development of autistic children to match more closely that of their normal peers. This approach could help rein in developmental deviations in children with autism, giving them the ability to recover lost skills as well as to gain new ones more quickly. For the parents of these children, who have had to helplessly watch them succumb to the symptoms of autism, this simple paradigm shift could provide a way to treat the disorder before the autistic metamorphosis is complete and the familiar baby they knew is lost to them forever.

The benefits of such a new, focused treatment for autism far outweigh the perceived risks. New drug treatments being developed that facilitate the function of serotonin, paired with behavioral therapies, hold the promise of a radically different developmental outcome for children with autism and, down the road, for children with other developmental disorders as well. ■

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