

Autism researchers are hot on the idea that autism results from abnormal communications between brain regions rather than a broken part of the brain

Autistic Brains Out of Synch?

Fourteen-year-old Benjamin Garbowit memorizes long lists of ingredients from food labels but has trouble understanding the point of even simple storybooks. The eighth grader from Short Hills, New Jersey, struggles through a conversation with a stranger, offering mostly one-word utterances. And he is confused by common gestures such as a pat on the head from his mother. "What does it mean?" he wants to know. "Is it love?"

Benjamin has autism, a disorder that has long mystified parents, doctors, and scientists alike because of the diverse deficits, and occasional talents, that accompany it. Although the most glaring problems appear in social interactions, serious shortcomings also show up in reasoning tasks that require integrating different types of information. Autistic individuals may memorize facts easily but find complex concepts elusive.

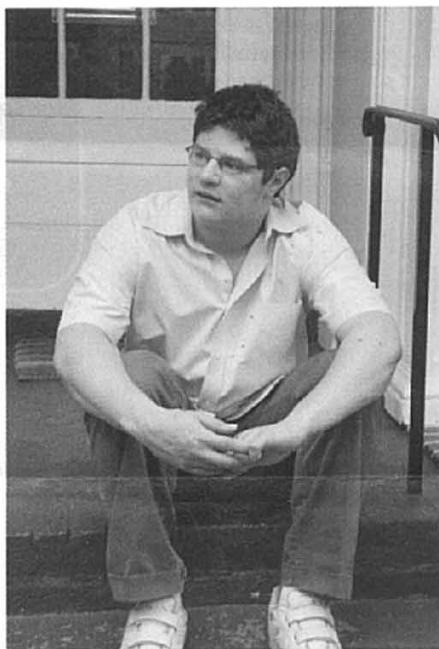
Researchers have struggled to find an overarching conception of the disorder. And in the past 3 years, they have accumulated tantalizing data suggesting that the problems in autism result from poor connections in the brain areas rather than from defects in a specific brain region. "A confluence of investigations point to a model of autism in which different brain regions are not talking to each other very well," says Martha Herbert, a pediatric neurologist at Harvard Medical School in Boston. "This is a big paradigm shift, because people have been looking for the 'brain address' of the problem in autism."

Imaging experiments show a lack of cooperation between different brain areas, as well as abnormalities in the volume and distribution of the white matter that insulates neuronal signals. Other studies have found oddities in the organization, number, and size of neurons in certain brain regions that could give rise to connectivity problems. "It's the most exciting set of developments in the field to date," comments Helen Tager-Flusberg, an autism researcher at Boston University School of Medicine.

So far, the studies are largely suggestive, and skeptics say that connectivity theory does not get to the bottom of autism. Yet if the theory is correct, it suggests a new approach to molecular studies of the dis-

ease. For instance, researchers might look for genes that perturb the development of neural connections rather than genes that map to specific behaviors.

Meanwhile, the work may enable more precise diagnosis of the disorder and a new way to test the efficacy of behavioral therapies or future drugs. "We're very close to finding a biological marker for autism using brain morphology and activation," says Marcel Just, a cognitive neuroscientist at Carnegie Mellon University in Pittsburgh, Pennsylvania.



Just the facts. Benjamin Garbowit, 14, knows the populations of many nations but struggles with the point of even simple stories.

Incommunicado

The idea that faulty connections are at the core of autism is implied in a psychological theory proposed in the 1980s by developmental neuropsychologist Uta Frith of University College London. Frith noted that many autistic behaviors can be explained by a person obsessing with details and not integrating the particulars—whether they be words, facts, or visual details—to determine their broader meaning. Frith theorized that

this tendency resulted from a lack of "top-down" mental processing. In the autistic brain, the theory went, the brain's frontal lobes—which play a central role in organizing, planning, directing attention, and guiding behavior—are not communicating properly with the more detail-oriented areas at the back of the brain.

It was not until 2002 that Frith and her colleagues reported the first evidence for connectivity problems in autism. The researchers used positron emission tomography (PET) to scan the brains of 10 high-functioning autistic people and 10 controls while they tried to interpret the actions of two triangles on a computer screen. Under different conditions, the triangles moved randomly, interacted in straightforward ways such as dancing or chasing, or appeared to use mental strategies such as coaxing or tricking that autistic people typically do not recognize.

As expected, the autistics did not describe the triangles' "intentions" as well as the normal subjects did, and they showed less activation in frontal brain regions involved in understanding the mental states of others. In addition, the scientists found that a visual region was not in synch with the mental-strategy network in the autistic brains, "as if there were some sort of bottleneck" in communications, Frith says.

The latest data, from functional magnetic resonance imaging (fMRI), suggest that other parts of the brain are on nonspeaking terms as well. (Unlike PET, in which brain activation in each area is averaged over the course of a task, fMRI samples activation levels as often as once a second, enabling researchers to correlate the patterns of activation of different brain regions in time.) Just's lab at Carnegie Mellon, along with Nancy Minshew at the University of Pittsburgh School of Medicine, imaged the brains of 17 high-functioning autistic people and 17 controls as they answered questions about sentences. During this task, the activated brain areas showed far less synchrony in the autistic brains than in the brains of controls, they reported last August in *Brain*. "Some of the regions aren't linked up," Minshew concludes.

When the Pittsburgh teams used fMRI to test the ability to remember faces, they saw more varied connectivity abnormalities. In the

autistic brains, links were weak between the front of the brain and the parietal lobe, between frontal regions and posterior perceptual brain areas, and between the face-processing brain region and other areas, the team reported in May at the International Meeting for Autism Research in Boston. They also described connectivity abnormalities in the brain network involved in the triangle task. "In study after study, we see a lower degree of synchronization in autistic brains," Just says.

This phenomenon could explain why autistic people have trouble carrying out certain actions. Ralph-Axel Müller, a cognitive neuroscientist at San Diego State University in California, and his colleagues recently scanned the brains of eight autistic males and eight controls while they watched an image of a hand on a computer screen. Each time a blue dot appeared on a finger, the subject tried to press a button with the same finger on his hand. As expected, the autistic males performed worse than controls. Their brains also showed a lack of synchrony between visual areas in the back of the brain and the inferior frontal cortex, which governs action planning and other functions. The results suggest that neural circuits for action plans may not be fully intact in autism, the researchers reported in the 15 April issue of *Neuroimage*.

Part of the communication failure could be with so-called mirror neurons, which are heavily involved in imitating behaviors (*Science*, 13 May, p. 945). "It appears that the mirror-neuron system is impaired in autism because the long fiber tracts that connect to the mirror neurons are not as well organized," Müller speculates. If so, that could explain the failure to imitate spoken words, for example, and might account for some of the language delays in autism.

Faulty wiring

Anatomical evidence is also bolstering the idea that disparate brain regions do not communicate efficiently in autism. For instance, Harvard's Herbert and her colleagues saw a large

excess of white matter, which contains the nerve fibers insulated with myelin, in the brains of 14 autistic boys aged 5 to 11 compared to 14 normal boys in a structural MRI study reported in the April 2004 *Annals of Neurology*. Frontal areas showed the greatest excesses. The pre-frontal lobe, the area devoted to the most complex processing, had 36% more white matter in the autistic brains compared to a 22% enlargement in the occipital lobe at the back of the brain, indicating that autistic brains sport irregularities in their white matter and particularly in the lobes that integrate different types of information.

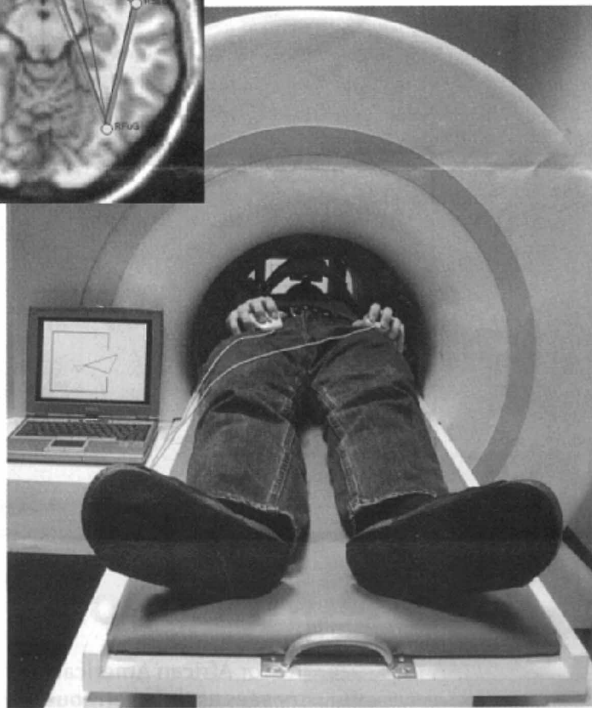
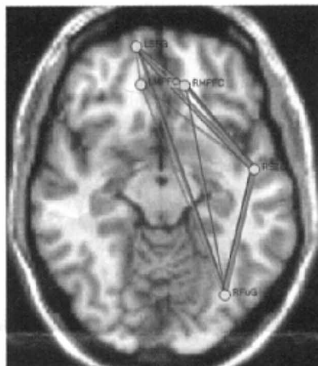
This surfeit of white matter was concentrated at the brain's surface, where short- and medium-range nerve fibers abound. Deeper, longer stretches of white matter, such as the nerve fibers that connect the two halves of the brain, were not enlarged in the autistic boys they examined. This suggests that individual brain regions—particularly the pre-frontal cortex, devoted to complex processing—may have hyperefficient internal communications but don't interact well with distant brain regions, such as those in the other hemisphere.

Herbert thinks the culprit may lie in the white matter itself, but it's too early to decide, she says, whether the abnormality relates to myelin production, neuronal fibers, or some other white-matter component. Herbert did not see any evidence of additional gray matter, which is dense with neurons, in the school-age autistic brains she studied.

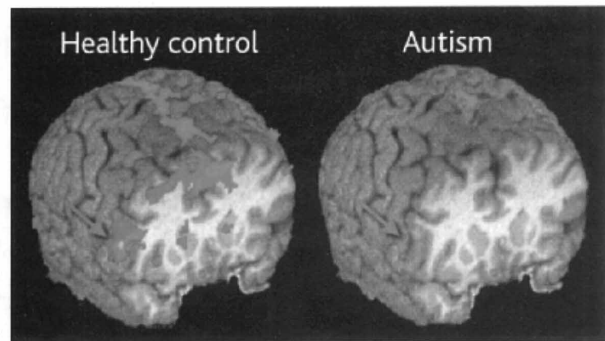
But others have found gray-matter abnormalities in autism, suggesting that the excess white matter might reflect a normal amount of wrapping on a larger number of nerve fibers. Autistic toddlers have on average 12% more gray matter in their cerebral cortex, according to a 2001 study by neuroscientist Eric Courchesne of the University of California, San Diego, and his colleagues. In unpublished postmortem studies, Courchesne's group has

found a large excess of a special class of pyramidal neurons in the frontal cortex.

Courchesne sees an imbalance in neuronal numbers between the front and back of the brain as a potential root cause of autism. If neurons that process sensory signals at the rear of the brain try to communicate with too many frontal neurons, their connections to that lobe may be too diffuse and lose their impact. That would greatly impair the ability



Dancing triangles. A volunteer tries to interpret the motives of two interacting triangles in an MRI simulator. (Inset) Autistic people show lower synchrony between areas of a brain network (blue lines) during this task than do controls (red lines).



Copycat smarts. The autistic brain (right) shows very little cooperation between brain areas when volunteers try to perform copycat finger movements. In controls (left), various brain regions, including the site of "mirror neurons" (arrow), work together during the exercise.

of the frontal cortex to integrate sensory information, direct attention, plan, organize, and perform its other functions.

The theory that autism results primarily from a gray-matter imbalance is also consistent with findings from the lab of neuroscientist Manuel Casanova, now at the University of Louisville School of Medicine in Kentucky. In 2002, Casanova and his colleagues published data showing abnormalities in postmortem autistic brains in cortical minicolumns. These are groups of 80 to 100 cells that extend inward from the brain's surface and function as information processing units. The nine autistic brains that Casanova's team examined had many more—but much smaller—minicolumns than nine control brains had in certain portions of the frontal and temporal lobes, the researchers reported in *Neurology*. Having more minicolumns would create an abundance of short connective fibers relative to

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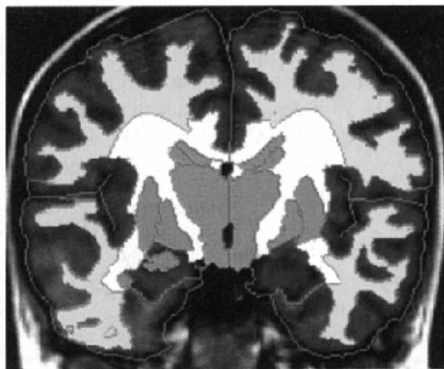
long ones, perhaps accounting for the disproportionate increase in white matter relative to gray matter in autistic brains.

And in unpublished findings from seven autistic and seven control brains, Casanova and Christoph Schmitz of the University of Maastricht in the Netherlands and their colleagues found that the autistic brains also had smaller cells in their minicolumns. Smaller cells carry shorter axons, bolstering the hypothesis that autism results from too many short-range connections and not enough long ones.

Even if a neuronal imbalance is to blame, no one knows how it arises. Courchesne and others hypothesize that it might result from a problem in the pruning, or elimination, of neurons and synapses early in life. Work from Courchesne's lab from 2003 suggests that most of the abnormal brain growth in autism occurs from birth to age 3. This may leave an unruly excess of neurons and circuitry in certain brain regions.

More questions than answers

Despite the converging evidence, not everyone is convinced that faulty connections lie at



Not too deep. Autistic brains contain an excess of surface white matter (yellow), which contains relatively short neuronal fibers, but do not show an enlargement of deeper white matter (white), where the longest fibers reside.

the heart of autism. Geraldine Dawson, an autism researcher at the University of Washington, Seattle, suggests that connectivity problems in autism might be an effect—rather than a cause—of an earlier dysfunction in the brain, such as a defect in brain systems that govern social reward and affect an infant's attention to faces and speech. Such a

defect, Dawson says, “will influence the development of speech and face perception, which ultimately will affect the development of the complex, integrated brain circuitry that underlies language and social development.”

Even if connectivity problems are at the root of autism, the theory needs fleshing out. Abnormalities in brain connectivity have also shown up in attention deficit hyperactivity disorder (ADHD), schizophrenia, and dyslexia. To get to the heart of autism, researchers now need to pinpoint which particular white matter—or gray matter—abnormalities are the problem in autism versus, say, dyslexia or ADHD, skeptics point out.

Even so, proponents argue that the theory at least points researchers in the right direction. “It’s a much more valid way of looking at impairments in autism. It’s where the field of autism has to go,” Müller says. And no matter where connectivity theory leads, the autism field is energized by the concept. Says Courchesne: “People smell something really exciting. They are seeing that there is a very interesting, if complex, story emerging.”

—INGRID WICKELGREN