At first glance you might not notice anything odd on meeting a young boy with autism. But if you try to talk to him, it will quickly become obvious that something is seriously wrong. He may not make eye contact with you; instead he may avoid your gaze and fidget, rock his body to and fro, or bang his head against the wall. More disconcerting, he may not be able to conduct anything remotely resembling a normal conversation. Even though he can experience emotions such as fear, rage and pleasure, he may lack genuine empathy for other people and be oblivious to subtle social cues that most children would pick up effortlessly.

In the 1940s two physicians—American psychiatrist Leo Kanner and Austrian pediatrician Hans Asperger—independently discovered this developmental disorder, which afflicts about 0.5 percent of American children. Neither researcher had any knowledge of the other’s work, and yet by an uncanny coincidence each gave the syndrome the same name: autism, which derives from the Greek word *autos*, meaning “self.” The name is apt, because the most conspicuous feature of the disorder is a withdrawal from social interaction. More recently, doctors have adopted the term “autism spectrum disorder” to make it clear that the illness has many related variants that range widely in severity but share some characteristic symptoms.

Ever since autism was identified, researchers have struggled to determine what causes it. Scientists know that susceptibility to autism is inherited, although environmental risk factors also seem to play a role [see “The Early Origins of Autism,” by Patricia M. Rodier; *Scientific American*].
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Overview/Mirror Neurons and Autism

- Because mirror neurons appear to be involved in social interaction, dysfunctions of this neural system could explain some of the primary symptoms of autism, including isolation and absence of empathy.
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making that movement. Brain-imaging techniques subsequently showed that these so-called mirror neurons also exist in the corresponding regions of the human cortex. These observations implied that mirror neurons—or, more accurately, the networks they are part of—not only send motor commands but also enable both monkeys and humans to determine the intentions of other individuals by mentally simulating their actions. In monkeys, the role of the neurons may be limited to predicting simple goal-directed actions, but in humans the mirror neuron system may have evolved the ability to interpret more complex intentions.

Later research showed that mirror neurons are located in other parts of the human brain, such as the cingulate and insular cortices, and that they may play a role in empathetic emotional responses. While studying the anterior cingulate cortex of awake human subjects, investigators found that certain neurons that typically fire in response to pain also fired when the person saw someone else in pain. Mirror neurons may also be involved in imitation, an ability that appears to exist in rudimentary form in the great apes but is most pronounced in humans. The propensity to imitate must be at least partly innate: Andrew Meltzoff of the University of Washington has shown that if you stick your tongue out at a newborn baby, the infant will do the same. Because the baby cannot see its own tongue, it cannot use visual feedback and error correction to learn the skill. Instead there must be a hardwired mechanism in the child’s brain for mapping the mother’s visual appearance—whether it be a tongue sticking out or a smile—onto the motor command neurons.

Language development in childhood also requires a remapping of sorts between brain areas. To imitate the mother’s or father’s words, the child’s brain must transform auditory signals in the hearing centers of the brain’s temporal lobes into verbal output from the motor cortex. Whether mirror neurons are directly involved in this skill is not known, but clearly some analogous process must be going on. Last, mirror neurons may enable humans to see themselves as others see them, which may be an essential ability for self-awareness and introspection.

Suppressing Mu Waves

What has all this to do with autism? In the late 1990s our group at U.C.S.D. noted that mirror neurons appear to be performing precisely the same functions that seem to be disrupted in autism. If the mirror neuron system is indeed involved in the interpretation of complex intentions, then a breakdown of this neural circuitry could explain the most striking deficit in people with autism, their lack of social skills. The other cardinal signs of the disorder—absence of empathy, language deficits, poor imitation, and so on—are also the kinds of things you would expect to see if mirror neurons were dysfunctional. Andrew Whitten’s group at the University of St. Andrews in Scotland made this proposal at about the same time we did, but the first experimental evidence for the hypothesis came from our lab, working in collaboration with Eric L. Altschuler and Jaime A. Pineda of U.C.S.D.

To demonstrate mirror neuron dysfunction in children with autism, we needed to find a way to monitor the activity of their nerve cells without putting electrodes in their brains (as Rizzolatti and his colleagues did with their monkeys). We realized that we could do so using an electroencephalogram (EEG) measurement of the children’s brain waves. For more than half a century, scientists have known that an EEG component called the mu wave is blocked anytime a person makes a voluntary muscle movement, such as opening and closing one’s hands. Interestingly, this component is also blocked when a person watches someone else perform the same
To study the mirror neuron system in people with autism, researchers relied on the observation that the firing of neurons in the premotor cortex suppresses the mu wave, a component of the electroencephalogram (EEG) measurement of the brain’s activity. (Mu waves range from eight to 13 hertz.) Investigators monitored the mu waves of children with autism and control subjects as they made voluntary muscle movements and then watched the same actions on video.

**TAking Action**

Motor command neurons fire whenever a person makes a voluntary muscle movement. Researchers asked all the subjects to open and close their right hands. In the children with autism and the control subjects, this action suppressed the amplitude of their mu waves, as expected.

**Simulating Action**

Mirror neurons in the premotor cortex also fire when a person observes someone else performing an action. The investigators took EEG measurements of brain activity while the subjects observed a video of a hand opening and closing. The mu waves of the control subjects plummeted (red), but those of the children with autism showed no suppression (blue). This finding suggests that the mirror neuron systems of the children with autism are deficient.
action. One of us (Ramachandran) and Altschuler suggested that mu-wave suppression might provide a simple, noninvasive probe for monitoring mirror neuron activity.

We decided to focus our first experiments on a high-functioning child with autism—that is, a child without severe cognitive impairments. (Very young, low-functioning children did not participate in this study because we wanted to confirm that any differences we found were not a result of problems in attention, understanding instructions or the general effects of mental retardation.) The EEG showed that the child had an observable mu wave that was suppressed when he made a simple, voluntary movement, just as in normal children. But when the child watched someone else perform the action, the suppression did not occur. We concluded that the child’s motor command system was intact but that his mirror neuron system was deficient. This observation, which we presented at the annual meeting of the Society for Neuroscience in 2000, provided a striking vindication of our hypothesis.

One has to be careful, however, of generalizing from a single case, so our lab group later conducted a more systematic series of experiments in 10 high-functioning individuals with autism spectrum disorder and 10 age- and gender-matched control subjects. We saw the expected suppression of mu waves when the control subjects moved their hands and watched videos of a moving hand, but the EEGs of the subjects with autism showed mu suppression only when they moved their own hands.

Other researchers have confirmed our results using different techniques for monitoring neural activity. A group led by Riitta Hari of the Helsinki University of Technology found mirror neuron deficits in children with autism by employing magnetoencephalography, which measures the magnetic fields produced by electric currents in the brain. More recently, Mirella Dapretto of the University of California, Los Angeles, and her colleagues used functional magnetic resonance imaging to show a reduction in mirror neuron activity in the prefrontal cortices of individuals with autism. And Hugo Théoret of the University of Montreal and his co-workers used transcranial magnetic stimulation, a technique that induces electric currents in the motor cortex to generate muscle movements, to study mirror neuron activity in subjects with autism. In the control subjects, induced hand movements became more pronounced when the subjects watched videos of the same movements; this effect was much weaker in the subjects with autism.

Taken together, these findings provide compelling evidence that people with autism have dysfunctional mirror neuron systems. Scientists do not yet know which genetic and environmental risk factors can prevent the development of mirror neurons or alter their function, but many research groups are now actively pursuing the hypothesis because it predicts symptoms that are unique to autism. In addition to explaining the primary signs of autism, deficiencies in the mirror neuron system can also account for some of the less well known symptoms. For instance, researchers have long known that children with autism often have problems interpreting proverbs and metaphors. When we told one of our subjects to “get a grip on yourself,” he took the message literally and started grabbing his own body. Though seen in only a subset of children with autism, this difficulty with metaphors cries out for an explanation.

Understanding metaphors requires the ability to extract a common denominator from superficially dissimilar entities. Consider the bouba/kiki effect, which was discovered by German-American psychologist Wolfgang Köhler more than 60 years ago. In this test, a researcher displays two crudely drawn shapes, one jagged and one curvy, to an audience and asks, “Which of these shapes is bouba and which is kiki?” No matter what languages the respondents speak, 98 percent will pick the curvy shape as bouba and the jagged one as kiki. This result suggests that the human brain is somehow able to extract abstract properties from the shapes and sounds—for example, the property of jaggedness embodied in both the pointy drawing and the harsh sound of kiki. We conjectured that this type of cross-domain mapping is analogous to metaphors and must surely involve neural circuits similar to those in the mirror neuron system. Consistent with this speculation, we discovered that children with autism perform poorly at the bouba/kiki test, pairing the shapes and sounds incorrectly.

But which part of the human brain is involved in this skill? The angular gyrus, which sits at the crossroads of the brain’s vision, hearing and touch centers, seemed to be a likely candidate—not only because of its strategic location but because nerve cells with mirror neuron-like properties have been identified there. When we studied nonautistic subjects with damage to this area of the brain, we found that many of them fail the bouba/kiki test and have a disproportionate dif-
difficulty understanding metaphors, just like people with autism. These results suggest that cross-domain mapping may have originally developed to aid primates in complex motor tasks such as grasping tree branches (which requires the rapid assimilation of visual, auditory and touch information) but eventually evolved into an ability to create metaphors. Mirror neurons allowed humans to reach for the stars, instead of mere peanuts.

Can the Mirrors Be Repaired?

The discovery of mirror neuron deficiencies in people with autism opens up new approaches to diagnosing and treating the disorder. For example, physicians could use the lack of mu-wave suppression (or perhaps the failure to mimic a mother sticking out her tongue) as a diagnostic tool to identify children with autism in early infancy, so that the currently available behavioral therapies can be started as quickly as possible. Timely intervention is critical; the behavioral therapies are much less effective if begun after autism’s main symptoms appear (typically between ages two and four).

An even more intriguing possibility would be to use biofeedback to treat autism or at least alleviate its symptoms. Doctors could monitor the mu waves of a child with autism and display them on a screen in front of the patient. If the child’s mirror neuron functions are dormant rather than completely lost, it may be possible for him or her to revive this ability by learning—through trial and error and visual feedback—how to suppress the mu waves on the screen. Our colleague Pineda is pursuing this approach, and his preliminary results look promising. Such therapies, though, should supplement rather than replace the traditional behavioral-training techniques.

Another novel therapeutic approach might rely on correcting chemical imbalances that disable the mirror neurons in individuals with autism. Our group (including students Mikhi Horvath and Mary Vertinsky) has suggested that specialized neuromodulators may enhance the activity of mirror neurons involved in emotional responses. According to this hypothesis, the partial depletion of such chemicals could explain the lack of emotional empathy seen in autism, and therefore researchers should look for compounds that stimulate the release of the neuromodulators or mimic their effects on mirror neurons. One candidate for investigation is MDMA, better known as ecstasy, which has been shown to foster emotional closeness and communication. It is possible that researchers may be able to modify the compound to develop a safe, effective treatment that could alleviate at least some of autism’s symptoms.

Such treatments, however, may offer only partial relief, because other symptoms of autism cannot be explained by the mirror neuron hypothesis—for example, repetitive motions such as rocking to and fro, avoidance of eye contact, hypersensitivity, and aversion to certain sounds. In an attempt to determine how these secondary symptoms might arise, our lab group (in collaboration with William Hirstein of Elmhurst College and Portia Iversen of Cure Autism Now, a nonprofit foundation based in Los Angeles) has developed what we call the salience landscape theory.

When a person looks at the world, he

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**THE SALIENCE LANDSCAPE THEORY**

To account for some of the secondary symptoms of autism—hypersensitivity, avoidance of eye contact, aversion to certain sounds, and so on—researchers have developed the salience landscape theory. In a typical child, sensory information is relayed to the amygdala, the gateway to the emotion-regulating limbic system. Using input from stored knowledge, the amygdala determines how the child should respond emotionally to each stimulus, creating a salience landscape of the child’s environment. In children with autism, though, the connections between the sensory areas and the amygdala may be altered, resulting in extreme emotional responses to trivial events and objects.

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**TYPICAL CHILD**

1. Sensory information is relayed to amygdala
2. Child exhibits appropriate emotional response
3. Heart pumping normally

**CHILD WITH AUTISM**

1. Altered connection between visual cortex and amygdala distorts child’s response
2. Amygdala triggers autonomous nervous system, raising heart rate
3. Child looks away to reduce distress
or she is confronted with an overwhelming amount of sensory information—sights, sounds, smells, and so on. After being processed in the brain’s sensory areas, the information is relayed to the amygdala, which acts as a portal to the emotion-regulating limbic system. Using input from the individual’s stored knowledge, the amygdala determines how the person should respond emotionally—for example, with fear (at the sight of a burglar), lust (on seeing a lover) or indifference (when facing something trivial). Messages cascade from the amygdala to the rest of the limbic system and eventually reach the autonomic nervous system, which prepares the body for action. If the person is confronting a burglar, for example, his heart rate will rise and his body will sweat to dissipate the heat from muscular exertion. The autonomic arousal, in turn, feeds back into the brain, amplifying the emotional response. Over time, the amygdala creates a salience landscape, a map that details the emotional significance of everything in the individual’s environment.

Our group decided to explore the possibility that children with autism have a distorted salience landscape, perhaps because of altered connections between the cortical areas that process sensory input and the amygdala or between the limbic structures and the frontal lobes that regulate the resulting behavior. As a result of these abnormal connections, any trivial event or object could set off an extreme emotional response—an autonomic storm—in the child’s mind. This hypothesis would explain why children with autism tend to avoid eye contact and any other novel sensation that might trigger an upheaval. The distorted perceptions of emotional significance might also explain why many children with autism become intensely preoccupied with trifles such as train schedules while expressing no interest at all in things that most children find fascinating.

We found some support for our hypothesis when we monitored autonomic responses in a group of 37 children with autism by measuring the increase in their skin conductance caused by sweating. In contrast with the control subjects, the children with autism had a higher overall level of autonomic arousal. Although they became agitated when exposed to trivial objects and events, they often ignored stimuli that triggered expected responses in the control group.

But how could a child’s salience landscape become so distorted? Investigators have found that nearly one third of children with autism have had temporal lobe epilepsy in infancy, and the proportion may be much higher given that many symptomatic therapy for autism. Hirstein is now developing a portable device that could monitor an autistic child’s skin conductance; when the device detects autonomic arousal, it could turn on another device, called a squeeze vest, that provides a comforting pressure by gently tightening around the child’s body.

Our two candidate theories for explaining the symptoms of autism—mirror neuron dysfunction and distorted salience landscape—are not necessarily contradictory. It is possible that the same event that distorts a child’s salience landscape—the scrambled connections between the limbic system and the rest of the brain—also damages the mirror neurons. Alternatively, the altered limbic connections could be a side effect of the same genes that trigger the dysfunctions in the mirror neuron system. Further experiments are needed to rigorously test these conjectures. The ultimate cause of autism remains to be discovered. In the meantime, our speculations may provide a useful framework for future research.

If the child’s mirror neuron functions are dormant rather than lost, it may be possible to revive this ability.

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