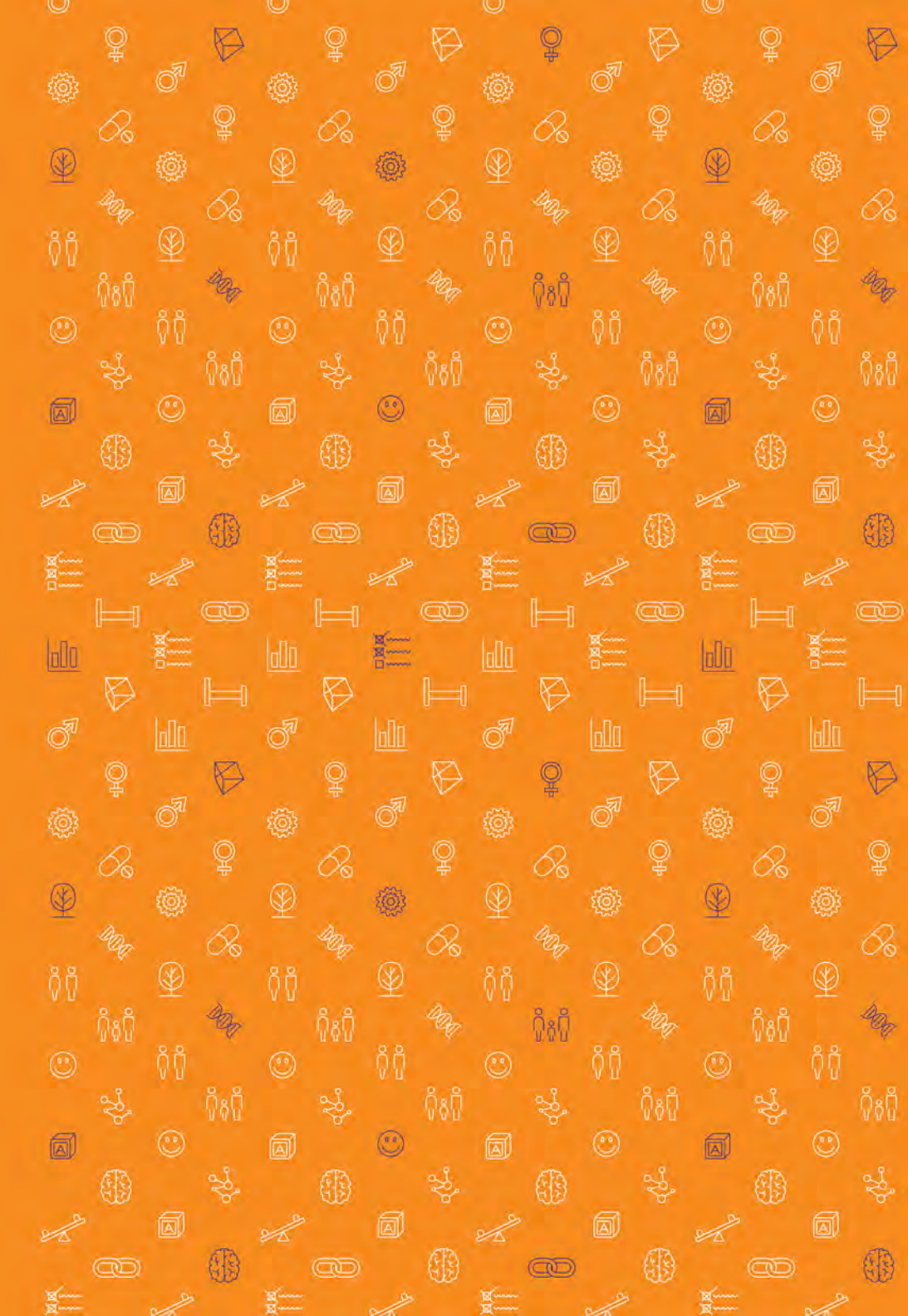




# SPECTRUM'S GUIDE TO AUTISM 2020





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AUTISM 2020**

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**Spectrum** has tracked autism research since our launch in 2008, covering evolving views of the condition's biology and lived experience. As scientists have gained more knowledge, these topics have become increasingly complex. So for this, our third, volume of *Spectrum* books, we went back to basics: Drawing on articles from the ever-expanding 'Autism 101' section of our website, we sought to create a guide to autism's landscape.

The first chapter aims to help readers navigate key questions about the condition: How is autism defined? Is its prevalence on the rise? What role does genetics play? Other articles lay out what research tells us about ongoing debates such as the role of environmental risk factors, parental age and a woman's use of antidepressants during pregnancy.

The second chapter explores more theoretical terrain: Some articles map out well-traveled research areas, such as the female protective effect, the extreme male brain theory and ideas about connectivity, multiple hits and signaling imbalances. Others venture onto newer conceptual paths, including serotonin's link to autism and a predictive coding theory of the condition.

The final chapter charts the clinical scene: How is a diagnosis established, and can genetic testing help? What hallmark traits and challenges come with autism, including problems with social communication and sleep? And what syndromes, such as Rett and fragile X, and other conditions, such as epilepsy and attention deficit hyperactivity disorder, often overlap with autism?

As research continues apace, *Spectrum* will continue to add to 'Autism 101' on our website—and redirect our coverage as needed. In the meantime, we hope this guide will help you find your way.

— *The Spectrum team*

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MALE



FEMALE



MUTATIONS



DRUGS



ENVIRONMENT



GENETICS



SEX



PARENTS



SEROTONIN



CONNECTIONS



CHILDHOOD



BRAIN



IMBALANCE



LINKS



DIAGNOSIS



SLEEP



DATA

**JUST THE  
FACTS**







5 May 2018

# The Evolution of 'autism' as a diagnosis

by Lina Zeldovich



illustration by MENGXIN LI

You can draw a straight line from the initial descriptions of many conditions—claustrophobia, for example, or vertigo—to their diagnostic criteria. Not so with autism. Its history has taken a less direct path with several detours, according to Jeffrey Baker, professor of pediatrics and history at Duke University in Durham, North Carolina.

Autism was originally described as a form of childhood schizophrenia and the result of cold parenting, then as a set of related developmental disorders, and finally as a spectrum condition with wide-ranging degrees of impairment.

Along with these shifting views, its diagnostic criteria have changed as well.

Here is how the Diagnostic and Statistical Manual of Mental Disorders (DSM), the diagnostic manual used in the United States, has reflected our evolving understanding of autism.



## Why was autism initially considered a psychiatric condition?

When Leo Kanner, an Austrian-American psychiatrist and physician, first described autism in 1943, he wrote about children with “extreme autistic aloneness,” “delayed echolalia” and an “anxiously obsessive desire for the maintenance of sameness.” He also noted that the children were often intelligent and some had extraordinary memory.

As a result, Kanner viewed autism as a profound emotional disturbance that does not affect cognition. In keeping with his perspective, the second edition of the DSM, the DSM-II, published in 1952, defined autism as a psychiatric condition—a form of childhood schizophrenia marked by a detachment from reality. During the 1950s and 1960s, autism was thought to be rooted in cold and unemotional mothers, whom Bruno Bettelheim dubbed ‘refrigerator mothers.’

## When was autism recognized as a developmental disorder?

The ‘refrigerator mother’ concept was disproved in the 1960s to 1970s, as a growing body of research showed that autism has biological underpinnings and is rooted in brain development. The DSM-III, published in 1980, established autism as its own separate diagnosis and described it as a “pervasive developmental disorder” distinct from schizophrenia.

Prior versions of the manual left many aspects of the diagnostic process open to clinicians' observations and interpretations, but the DSM-III listed specific criteria required for a diagnosis. It defined three essential features of autism: a lack of interest in people, severe impairments in communication and bizarre responses to the environment, all developing in the first 30 months of life.

## How long did this definition last?

The DSM-III was revised in 1987, significantly altering the autism criteria. It broadened the concept of autism by adding a diagnosis at the mild end of the spectrum—pervasive developmental disorder-not otherwise specified (PDD-NOS)—and dropping the requirement for onset before 30 months.

Even though the manual did not use the word 'spectrum,' the change reflected the growing understanding among researchers that autism is not a single condition but rather a spectrum of conditions that can present throughout life.

The updated manual listed 16 criteria across the three previously established domains, 8 of which had to be met for a diagnosis. Adding PDD-NOS allowed clinicians to include children who didn't fully meet the criteria for autism but still required developmental or behavioral support.



**THE DSM-II,  
PUBLISHED IN  
1952, DEFINED  
AUTISM AS A  
PSYCHIATRIC  
CONDITION.**

## When was autism first presented as a spectrum of conditions?

The DSM-IV, released in 1994 and revised in 2000, was the first edition to categorize autism as a spectrum.

This version listed five conditions with distinct features. In addition to autism and PDD-NOS, it added 'Asperger's disorder,' also at the mild end of the spectrum; 'childhood disintegrative disorder (CDD),' characterized by severe developmental reversals and regressions; and Rett syndrome, affecting movement and communication, primarily in girls. The breakdown echoed the research hypothesis at the time that autism is rooted in genetics, and that each category would ultimately be linked to a set of specific problems and treatments.

## Why did the DSM-5 adopt the idea of a continuous spectrum?

Throughout the 1990s, researchers hoped to identify genes that contribute to autism. After the Human Genome Project was completed in 2003, many studies tried to zero in on a list of 'autism genes.' They found hundreds, but could not link any exclusively to autism. It became clear that finding genetic underpinnings and corresponding treatments for the five conditions specified in the DSM-IV wouldn't be possible. Experts decided it would be best to characterize autism as an all-inclusive diagnosis, ranging from mild to severe.



At the same time, there was growing concern about a lack of consistency in how clinicians in different states and clinics arrived at a diagnosis of autism, Asperger syndrome or PDD-NOS. A spike in autism prevalence in the 2000s suggested that clinicians were sometimes swayed by parents lobbying for a particular diagnosis or influenced by the services available within their state.

To address both concerns, the DSM-5 introduced the term ‘autism spectrum disorder.’ This diagnosis is characterized by two groups of features: “persistent impairment in reciprocal social communication and social interaction” and “restricted, repetitive patterns of behavior,” both present in early childhood. Each group includes specific behaviors, a certain number of which clinicians have to identify. The manual eliminated Asperger syndrome, PDD-NOS and classic autism, but debuted a diagnosis of social communication disorder to include children with only language and social impairments. Childhood disintegrative disorder and Rett syndrome were removed from the autism category.



## Why did the DSM-5 spawn so much concern and controversy?

Even before the manual was released in 2013, many people with autism and their caregivers worried about its effect on their lives. Many were concerned that after their diagnosis disappeared from the book, they would lose services or insurance coverage. Those who identified themselves as having Asperger syndrome said the diagnosis gave them a sense of



belonging and an explanation for their challenges; they feared that removing the diagnosis was synonymous to losing their identity. And experts disagreed on whether the DSM-5's more stringent diagnostic criteria would block services for those with milder traits or adequately curb surging prevalence rates.

Five years later, it's clear the DSM-5 did not cut services for people already diagnosed with an autism spectrum condition. A growing body of evidence, however, shows that its criteria do exclude more people with milder traits, girls and older individuals than the DSM-IV did.

## Are there alternatives to the DSM?

Clinicians in many countries, including the United Kingdom, use the International Classification of Diseases. Released in the 1990s, that manual's current and 10th edition groups autism, Asperger syndrome, Rett syndrome, CDD and PDD-NOS together in a single 'Pervasive Developmental Disorders' section, much as the DSM-IV did.



**EXPERTS  
CONTINUE  
TO VIEW  
AUTISM AS A  
CONTINUOUS  
SPECTRUM OF  
CONDITIONS.**

# What does the future look like for diagnosing autism?

Experts continue to view autism as a continuous spectrum of conditions. There are no planned revisions to the DSM for now, but the language in a draft of the ICD-11—which is expected to debut in May 2018—mirrors the DSM-5’s criteria. In the ICD-11, autism criteria move to a new, dedicated ‘Autism Spectrum Disorder’ section.

The ICD-11 differs from the DSM-5 in several key ways. Instead of requiring a set number or combination of features for a diagnosis, it lists identifying features and lets clinicians decide whether an individual’s traits match up. Because the ICD is intended for global use, it also sets broader, less culturally specific criteria than the DSM-5 does. For instance, it puts less emphasis on what games children play than whether they follow or impose strict rules on those games. The ICD-11 also makes a distinction between autism with and without intellectual disability, and highlights the fact that older individuals and women sometimes mask their autism traits.





3 SEPTEMBER 2020

# Autism prevalence in the United States

by Jessica Wright



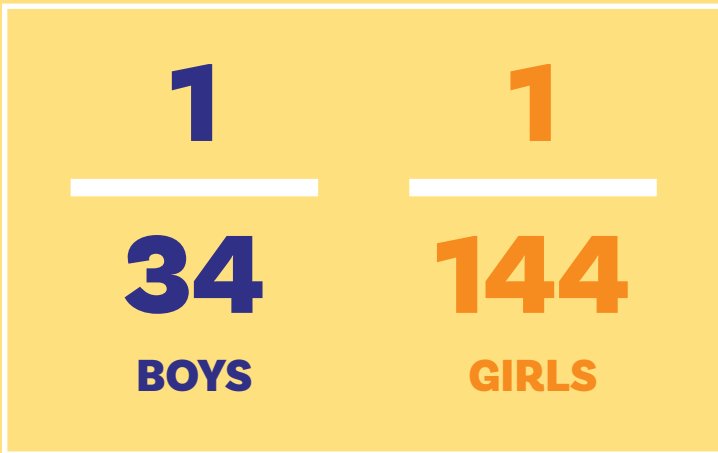
illustration by BEE JOHNSON

The prevalence of autism in the United States has risen steadily since researchers first began tracking it in 2000. The rise has sparked fears of an autism ‘epidemic.’ But experts say the bulk of the increase stems from a growing awareness of autism and changes to the condition’s diagnostic criteria.

Here’s how researchers track autism’s prevalence and explain its apparent rise.



# 1 IN 54 CHILDREN IN THE U.S.



≈ 4.3 BOYS FOR EVERY GIRL

## How do clinicians diagnose autism?

There is no blood test, brain scan or any other objective test that can diagnose autism—although researchers are actively trying to develop such tests. Clinicians rely on observations of a person’s behavior to diagnose the condition.

In the U.S., the criteria for diagnosing autism are laid out in the “Diagnostic and Statistical Manual of Mental Disorders” (DSM). The criteria are problems with social communication and interactions, and restricted interests or repetitive behaviors. Both of these ‘core’ traits must be present in early development.

## What is the prevalence of autism in the U.S.?

The Centers for Disease Control and Prevention (CDC) estimates that 1 in 54 children in the U.S. have autism. The prevalence is 4.3 times higher among boys than girls.

## How does the CDC arrive at this number?

CDC researchers collect health and school records for 8-year-old children who live in select U.S. counties. These researchers are part of the Autism and Developmental Disabilities Monitoring Network, which the CDC set up in 2000 to estimate autism prevalence.



Every two years, trained clinicians scan the records for signs of autism features, such as social problems or repetitive behaviors. They focus on 8-year-olds because most children are enrolled in school and have had routine health assessments by that age. They then decide whether each child meets the criteria for autism, even if the child does not have a diagnosis, and extrapolate the results to all children in the state.

The most recent prevalence estimates are based on data collected in 2016 from sites in 11 states. At some of the sites, clinicians also surveyed the records of 4-year-old children. These data suggest that autism prevalence among preschoolers is increasing, and mirrors both the rise and the overall prevalence among 8-year-olds.

The CDC is also launching a pilot program to look at autism in adolescents. Its researchers plan to review the records of 16-year-olds who were identified as having autism traits at age 8.



## How has autism prevalence changed over time?

The latest estimate of autism prevalence—1 in 54—is up 10 percent from the 1 in 59 estimate, based on data collected in 2014, and is more than double the 1 in 150 figure reported in 2000. In fact, the trend has been steeply upward since the early 1990s, not only in the U.S. but globally, says Maureen Durkin, who heads the network site in Wisconsin.



## How accurate is the CDC's approach?

The strength of the approach is that it takes a snapshot of all children who live in a certain area, not just those who have a diagnosis, according to Eric Fombonne, professor of psychiatry at Oregon Health and Science University in Portland. But, he notes, relying on school and medical records is not as accurate as assessing a child in person.

The approach also misses children who have no school or medical records, including some who are home-schooled or live in isolated regions. And children within the monitored areas may not be representative of all children in a state. Reported prevalence for autism can also vary dramatically between states, probably reflecting varying levels of autism awareness and of services offered.

Two national surveys conducted in 2016—in which researchers asked parents whether a healthcare provider had ever told them their child has autism—turned up a higher estimate of the condition's prevalence: 1 in 40. However, parent surveys are generally considered less reliable than the CDC's approach.

## Has our definition of autism changed over the years?

How people think about and diagnose autism has changed substantially since the diagnosis was first introduced nearly 75 years ago. In 1943, Leo Kanner first coined the term 'infantile autism' to describe children who seemed socially isolated and withdrawn.



In 1966, researchers estimated that about 1 in 2,500 children had autism, according to criteria derived from Kanner's description. This and other early estimates of prevalence probably focused on children at the severe end of the spectrum and missed those with subtler features.

Autism didn't make its debut in the DSM until 1980. In 1987, a new edition expanded the criteria by allowing a diagnosis even if symptoms became apparent after 30 months of age. To garner a diagnosis, a child needed to meet 8 of 16 criteria, rather than all 6 of the previous items. These changes may have caused the condition's prevalence to tick above 1 in 1,400.

Then, in 1991, the U.S. Department of Education ruled that a diagnosis of autism qualifies a child for special education services. Before this time, many children with autism may instead have been listed as having intellectual disability. The change may have encouraged families to get a diagnosis of autism for their child. The number of children who have both a diagnosis of autism and intellectual disability has also risen steadily over the years.

In 1994, the fourth edition of the DSM broadened the definition of autism even further, by including Asperger syndrome on the milder end of the spectrum. The current version, the DSM-5, was released in 2013, and collapsed autism, Asperger syndrome and pervasive developmental disorder—not otherwise specified into a single diagnosis.

## Has the rising awareness of autism contributed to the prevalence?

Increased awareness of autism has undoubtedly contributed to its rise in prevalence, Durkin says.

Until the 1980s, many people with autism were institutionalized, rendering them effectively invisible. Studies show that parents who are aware of autism's presentation—by living near someone with the condition, for example—are more likely to seek a diagnosis for their children than parents with no knowledge of the condition. Living close to urban centers and having access to good medical care also boost the likelihood of diagnosis.

Greater awareness of autism is also likely to boost CDC estimates by increasing the chances that autism traits, such as lack of eye contact, show up in school and medical records, says Fombonne.

Policy changes may have also played a role. In 2006, the American Academy of Pediatrics recommended screening all children for autism during routine pediatrician visits at 18 and 24 months of age. This move may have led to diagnoses for children who would otherwise have slipped under the radar.

## Are there other factors that have influenced prevalence?

Many individuals diagnosed with autism may, in the past, have been misdiagnosed with other conditions, such as intellectual disability. As diagnoses of autism have risen, those of intellectual disability have decreased.



# 1943

Leo Kanner  
coined the term  
'infantile autism'

# 1966

An estimated  
1 in 2,500  
children had  
autism

# 1980

Autism debuts  
in the DSM

# 1986

Expanded DSM  
criteria: 1 in 4,500  
prevalence

# 1991

U.S. Department  
of Education:  
autism = special  
education services

# 1994

The fourth edition  
of the DSM broadened  
the definition of  
autism further

# 2013

DSM-5 collapsed  
autism and Asperger  
syndrome into  
single diagnosis

What's more, a diagnosis of autism gives children greater access to specialized services and special education than do diagnoses of other conditions. This benefit makes clinicians more likely to diagnose a child with autism, even those who are on the borderline of the clinical criteria.

Prior versions of the DSM did not allow for children to be diagnosed with both autism and attention deficit hyperactivity disorder. The DSM-5 allows multiple diagnoses, and most children with developmental delay are routinely screened for autism.

Autism prevalence has traditionally been highest in white children in the U.S., but this is starting to change. African-American and Hispanic children have lower rates of diagnosis because of a lack of access to services. Widespread screening has improved detection of autism in these groups, and raised overall prevalence.

## Is there no real increase in autism rates, then?

Awareness and changing criteria probably account for the bulk of the rise in prevalence, but biological factors might also contribute, says Durkin. For example, having older parents, particularly an older father, may boost the risk of autism. Children born prematurely also are at increased risk of autism, and more premature infants survive now than ever before.





13 JUNE 2018

# Autism's sex ratio

by Nicholette Zeliadt



illustration by FRANZISKA BARCZYK

Autism is significantly more common in boys than in girls. This skewed sex ratio has been recognized since the first cases of autism were described in the 1940s. The exact reasons for the ratio remain unclear. It could be rooted in biological differences between the sexes. Or, some experts say, it may be an artifact of the way autism is defined and diagnosed.

Here's how researchers estimate and explain the sex ratio in autism.



## What is the sex ratio for autism?

Researchers have consistently found more boys than girls with autism when estimating the condition's prevalence. This has been true regardless of whether the data came from parent-reported diagnoses, reviews of school and medical records, or diagnostic evaluations of children.

The most comprehensive analysis of autism's sex ratio, published in 2017, drew on data from 54 prevalence studies worldwide. That analysis estimated about 4.2 boys with autism for every girl.

## What factors might alter this sex ratio?

One potentially important factor is diagnostic bias: Several studies suggest that girls receive autism diagnoses later in life than boys, indicating that the condition is harder to spot in girls.

In line with this idea, the 2017 study revealed that the sex ratio falls to 3.25 boys per girl when the analysis includes only the 20 studies in which researchers evaluated the participants for autism, rather than relying on previous diagnoses. This drop in the ratio provides the most compelling evidence yet for a diagnostic bias, says the study's lead investigator William Mandy, senior lecturer in clinical psychology at University College London. "It implies that there's a group of females out there who, if you assess them, will meet criteria, but for whatever reason they're not getting assessed."



## Why are girls and women with autism being overlooked?

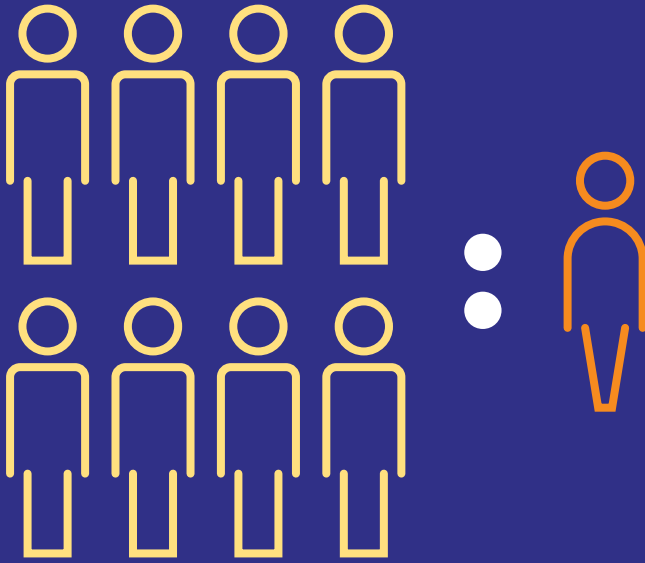
Girls and women with autism may go undiagnosed because doctors, teachers, parents and others often think of the condition as primarily affecting boys.

Autism may also look different in girls than it does in boys. Girls may have fewer restricted interests and repetitive behaviors than boys do, and may have more socially acceptable types of interests. They are also more likely than boys to mask their autism features by copying their neurotypical peers. As a result, autism may be more difficult to detect in girls even when doctors are looking for it.

## Would the sex ratio disappear if these diagnostic biases could be overcome?

Probably not. Researchers have found a 3-to-1 ratio even when they have followed children from infancy and repeatedly screened them for autism, minimizing the possibility for biases in diagnosis and referral. The children in these studies have a family history of autism, however, so they may be fundamentally different from other children with the condition, says Daniel Messinger, professor of psychology at the University of Miami.





**1995**



**2010**

## Has the sex ratio changed over time?

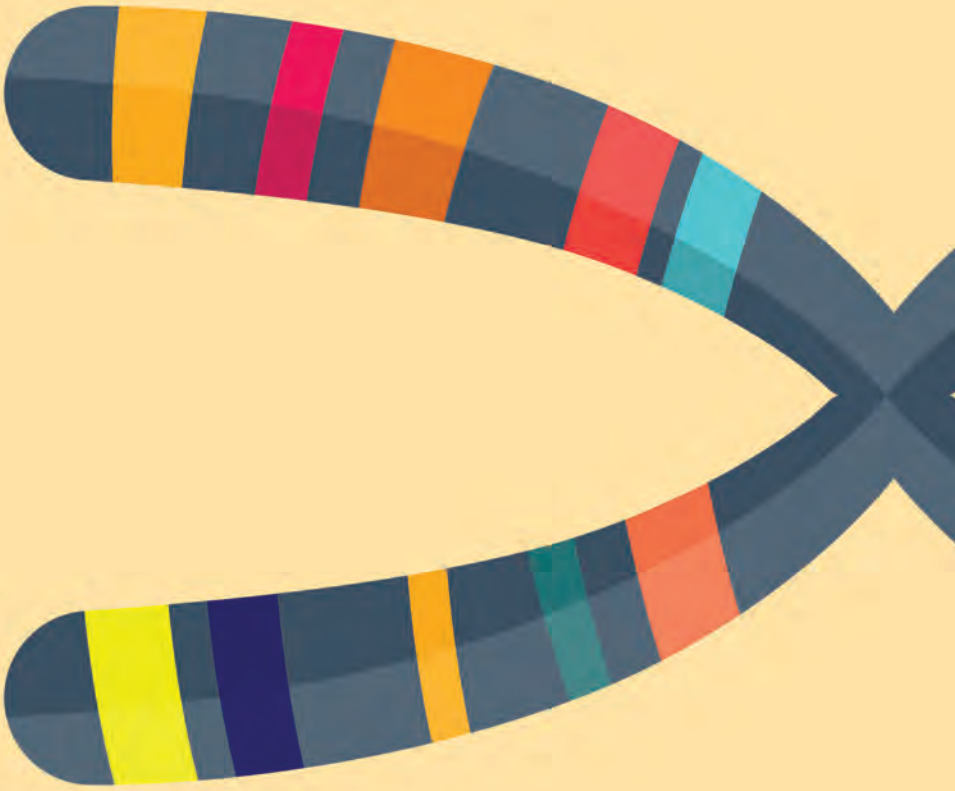
Yes. A large Danish study found an 8-to-1 sex ratio for autism in 1995, but that had dropped to 3-to-1 by 2010. The drop may reflect better detection of girls with autism, but is likely to level off. “I would put my money on 3-to-1,” says Meng-Chuan Lai, assistant professor of psychiatry at the University of Toronto.

## What else could explain the sex ratio?

Biology. For example, the brains of people with autism show patterns of gene expression that look more like those of typical males than typical females. Some of these genes are specific to microglia, immune cells in the brain that clear away debris and sculpt neuronal connections.

It is also possible that girls are somehow shielded from the condition. Girls with autism tend to have more mutations than boys with the condition. And boys with autism seem to inherit their mutations from unaffected mothers more often than from unaffected fathers. Together, these results suggest that girls need a bigger genetic hit than boys to have autism.





27 JUNE 2017

# Autism genetics

by Nicholette Zeliadt



illustration by YULIYA LESOVAYA / iStock

Researchers have known that genes contribute to autism since the 1970s, when a team found that identical twins often share the condition. Since then, scientists have been racking up potential genetic culprits in autism, a process that DNA-decoding technologies have accelerated in the past decade.

As this work has progressed, scientists have unearthed a variety of types of genetic changes that can underlie autism. The more scientists dig into DNA, the more intricate its contribution to autism seems to be.



## How do researchers know genes contribute to autism?

Since the first autism twin study in 1977, several teams have compared autism rates in twins and shown that autism is highly heritable. When one identical twin has autism, there is about an 80 percent chance that the other twin has it too. The corresponding rate for fraternal twins is around 40 percent.

However, genetics clearly does not account for all autism risk. Environmental factors also contribute to the condition—although researchers disagree on the relative contributions of genes and environment. Some environmental risk factors for autism, such as exposure to a maternal immune response in the womb or complications during birth, may work with genetic factors to produce autism or intensify its features.

## Is there such a thing as an autism gene?

Not really. There are several conditions associated with autism that stem from mutations in a single gene, including fragile X and Rett syndromes. But less than 1 percent of non-syndromic cases of autism stem from mutations in any single gene. So far, at least, there is no such thing as an ‘autism gene’—meaning that no gene is consistently mutated in every person with autism. There also does not seem to be any gene that causes autism every time it is mutated.

Still, the list of genes implicated in autism is growing. Researchers have tallied about 100 genes they consider strongly linked to autism. Many of these genes are important for communication between neurons or control the expression of other genes.

## How do these genes contribute to autism?

Changes, or mutations, in the DNA of these genes can lead to autism. Some mutations affect a single DNA base pair, or 'letter.' In fact, everyone has thousands of these genetic variants. A variant that is found in 1 percent or more of the population is considered 'common' and is called a single nucleotide polymorphism, or SNP.

Common variants typically have subtle effects and may work together to contribute to autism. 'Rare' variants, which are found in less than 1 percent of people, tend to have stronger effects. Many of the mutations linked to autism so far have been rare. It is significantly more difficult to find common variants for autism risk, although some studies are underway.

Other changes, known as copy number variations (CNVs), show up as deletions or duplications of long stretches of DNA and often include many genes.

But mutations that contribute to autism are probably not all in genes, which make up less than 2 percent of the genome. Researchers are trying to wade into the remaining 98 percent of the genome to look for irregularities associated with autism. So far, these regions are poorly understood.



## Are all mutations equally harmful?

No. At the molecular level, the effects of mutations may differ, even among SNPs. Mutations can be either harmful or benign, depending on how much they alter the corresponding protein's function. A missense mutation, for example, swaps one amino acid in the protein for another. If the substitution doesn't significantly change the protein, it is likely to be benign. A nonsense mutation, on the other hand, inserts a 'stop' sign within a gene, causing protein production to halt prematurely. The resulting protein is too short and functions poorly, if at all.

## How do people acquire mutations?

Most mutations are inherited from parents, and they can be common or rare. Mutations can also arise spontaneously in an egg or sperm, and so are found only in the child and not in her parents. Researchers can find these rare 'de novo' mutations by comparing the DNA sequences of people who have autism with those of their unaffected family members. Spontaneous mutations that arise after conception are usually 'mosaic,' meaning they affect only some of the cells in the body.



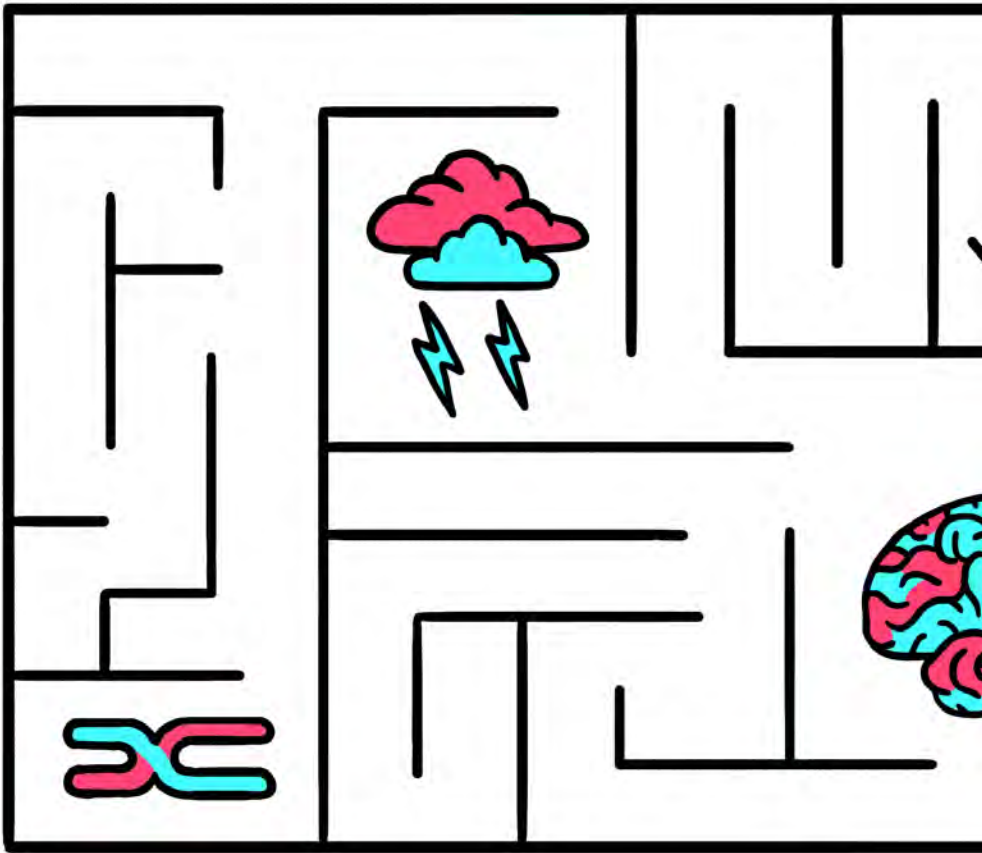
## Can genetics explain why boys are more likely than girls to have autism?

Perhaps. Girls with autism seem to have more mutations than do boys with the condition. And boys with autism sometimes inherit their mutations from unaffected mothers. Together, these results suggest that girls may be somehow resistant to mutations that contribute to autism and need a bigger genetic hit to have the condition.

## Is there a way to test for mutations before a child is born?

Clinicians routinely screen the chromosomes of a developing baby to identify large chromosomal abnormalities, including CNVs. There are prenatal genetic tests for some syndromes associated with autism, such as fragile X syndrome. But even if a developing baby has these rare mutations, there is no way to know for sure whether he will later be diagnosed with autism.





5 NOVEMBER 2018

# Environmental risk for autism

by Sarah DeWeerd

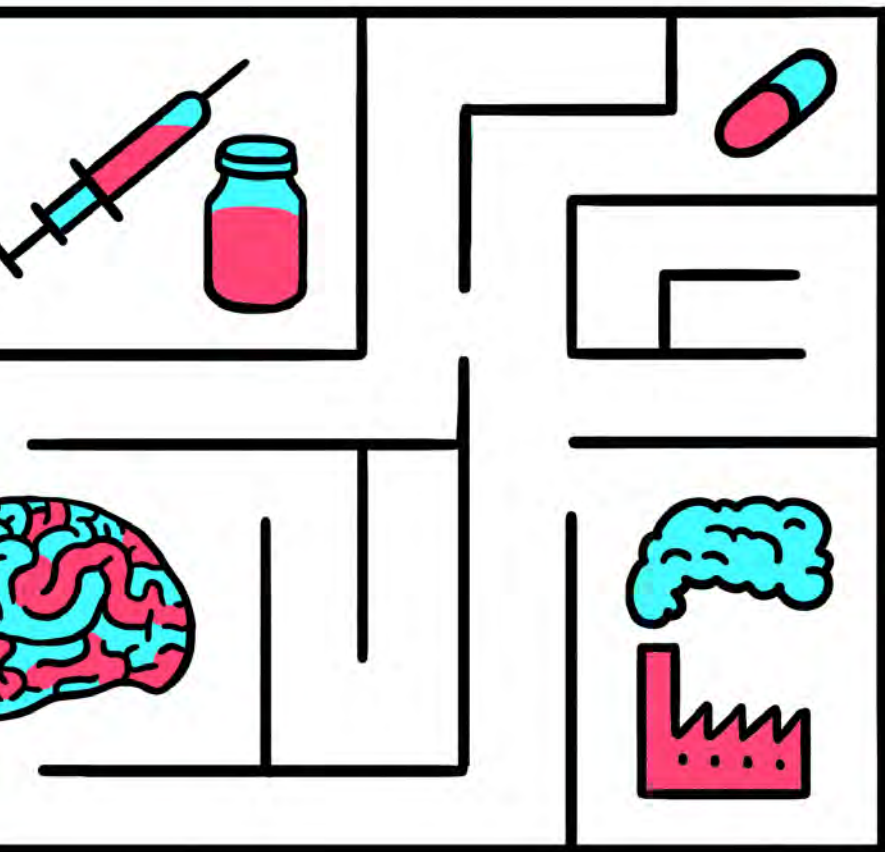


illustration by LAURÈNE BOGLIO

Autism results from an interplay between genetics and the environment. Dozens of genes have been implicated in the condition, but on the environmental side of the equation, it has been tough to nail down the factors involved.

Here, we explain why it is difficult to link autism to environmental factors, and what scientists know about how the environment influences autism risk.



## What qualifies as an environmental risk factor?

The term 'environmental risk factor' is usually understood to mean the chemicals or pollutants a person is exposed to. But scientists use a broader definition: An environmental risk factor is anything that alters the likelihood of having a condition and isn't encoded in an individual's DNA.

Environmental risk factors for autism include being born prematurely, soon after an older sibling or to a mother with diabetes, for example. Over the past 15 years or so, scientists have investigated many of these factors to determine how they may contribute to autism. But there's still little definitive information.

## Why don't we know which environmental factors increase risk for autism?

Studies of the environment's link to autism have returned inconsistent results. For example, some studies suggest that taking antidepressants during pregnancy increases autism risk in the child; others find no such link.

Most research on environmental risk comprises epidemiological studies, which identify associations between something in the environment and the likelihood of a diagnosis in large groups of people. But those studies do not demonstrate cause and effect.

For one thing, they are rife with what scientists call 'con-

founding factors’—variables that tend to travel together and make it difficult to pinpoint causal relationships.

What’s more, the causal relationships can be unclear. For example, we know that children with older fathers are more likely to have autism than those who have younger fathers. But we don’t know whether advanced paternal age itself increases autism risk or whether men who carry more genetic risk factors for autism, and perhaps display traits of the condition, tend to have children later in life.

Environmental factors are also often difficult to measure. Parents may be unaware of, or forget, what they and their child were exposed to. Or they may attach outsized importance to any detail they think could explain their child’s autism.

## Which environmental risk factors for autism are well established?

The most widely accepted risk factors operate during gestation or around the time of birth. Various pregnancy and birth complications are associated with an increased risk of autism. These include preterm birth, low birth weight and maternal diabetes or high blood pressure during pregnancy. Scientists are not sure of the mechanisms underlying these associations.

The maternal immune system appears to play a role in autism risk. Infections, serious illnesses, such as a bad case of influenza, and hospitalizations during pregnancy are all linked to an increased risk of autism in a child. Women with autoimmune diseases, in which the body attacks its own tissues, are also at an elevated risk of having an autistic child. And animal



**AUTISM  
RESULTS  
FROM AN  
INTERPLAY  
BETWEEN  
GENETICS  
AND THE  
ENVIRONMENT.**

studies suggest that certain immune molecules can alter gene expression and brain development in ways that may be relevant to autism.

Exposure to the drug valproate, which is used to treat bipolar disorder and epilepsy, in the womb is known to increase the risk of autism, as well as a variety of birth defects.

## What other factors are scientists investigating?

Scientists are still trying to tease apart the effects of maternal antidepressant use during pregnancy from those of depression itself.

One reason this issue has been difficult to settle is that if a parent has a brain condition, his or her child may carry shared genetic factors that increase autism risk.

Evidence that exposure to air pollution during gestation or early life increases a child's risk of autism has grown more robust over the past few years. Still, many questions remain, such as which of the many components of air pollution might be involved.

## Which proposed risk factors have been ruled out?

Despite the links between maternal immune factors and autism, routine vaccinations given during pregnancy, such as those against influenza and whooping cough, do not appear to boost autism risk.



Childhood vaccines are similarly in the clear. The research that purported to show a causal link was fraudulent and has been retracted, and no reliable evidence has ever emerged to support it. Scientists have also exonerated smoking during pregnancy as a contributor to autism. Of course, smoking during pregnancy is harmful for many other reasons.

## Are there any environmental factors that lower the risk of autism?

Scientists are trying to identify environmental risk factors for autism so that they can find a way to lower the risk. But the factors backed by the strongest evidence are not easy to modify.

Some studies suggest that taking vitamin D and vitamin B-9, or folic acid, supplements during pregnancy can decrease the baby's autism risk. But the evidence is not definitive.

## What are scientists doing to find out more?

New statistical techniques are helping scientists tackle confounding factors and draw more robust conclusions from epidemiological studies. Animal studies provide evidence about the mechanisms by which particular factors increase or decrease autism risk. And several efforts, such as the Environmental Influences on Child Health Outcomes study and the Early Markers for Autism study, are tracking environmental exposures and risk factors in children, starting before birth.



## What should parents and prospective parents do?

Families who are at high risk of having a child with autism—because they already have one child with the condition, for example—should consult with their doctor or a genetic counselor for specific recommendations. For most people, though, the general recommendations given to pregnant women (get a flu shot, take prenatal vitamins ) are unlikely to cause harm and may even help.

It's also important to remember that even for environmental factors that do appear to increase autism risk, the absolute risk of having a child with autism is small. For example, a large 2014 study of women in Sweden revealed that having an infection during pregnancy increases the risk of having a child with autism from 1 percent to 1.3 percent.





29 NOVEMBER 2017

# The link between parental age and autism

by Sarah DeWeerd



illustration by PEP BOATELLA

Older men and women are more likely than young ones to have a child with autism, according to multiple studies published in the past decade. Especially when it comes to fathers, this parental-age effect is one of the most consistent findings in the epidemiology of autism.

The link between a mother's age and autism is more complex: Women seem to be at increased odds of having a child with autism both when they are much older and much younger than average, according to some studies. Nailing down why either parent's age influences autism risk has proved difficult, however.

## How do we know that older men have elevated odds of fathering a child with autism?

Epidemiologists have gathered data on large numbers of families and calculated how often men of different ages have a child with autism. The first rigorous study of this type, published in 2006, drew on medical records of 132,000 Israeli adolescents. It showed that men in their 30s are 1.6 times as likely to have a child with autism as men under 30. Men in their 40s have a sixfold increase.

Since then, scientists have conducted similar analyses of data on children born in California, Denmark and Sweden, as well as of an international dataset on 5.7 million children. Nearly all of this research has shown an increased prevalence of autism among the children of older fathers.

## At what age do the odds of fathering a child with autism increase for men?

No one knows. The age ranges and ages of the men differ across studies, making their results hard to compare. Overall, the findings indicate that the odds increase steadily over time rather than suddenly rising after a certain age.

## How big is the increase?

The results of studies vary from 5 to 400 percent. One 2017 study based on whole-genome sequencing of nearly 5,000 people suggests that parents in their mid-40s are 5 to 10 percent more likely to have a child with autism than are 20-year-old parents.

But a large 2014 study based on Swedish medical records hinted that the odds of autism among children born to fathers older than 45 are about 75 percent higher than for children born to fathers in their early 20s. And a 2010 analysis of Swedish data found that men over 55 are four times as likely to have a child with autism as men under 30.

Even so, the absolute chance of having a child with autism is low even for the oldest parents. The researchers in the 2017 study calculated that about 1.5 percent of children born to parents in their 20s will have autism, compared with about 1.58 percent of children born to parents in their 40s.

## Why do older men have higher odds of fathering children with autism?

The most prominent hypothesis is that the sperm of older men has accumulated many spontaneous mutations that the men pass along to their children.

Sperm divide more often than egg cells do. With each division, a cell's DNA is copied, presenting an opportunity for mutations to occur. One study in Iceland showed that spontaneous, or de novo, mutations accumulate more rapidly in men



than in women. Another study in the same country suggested that with each passing year, a man transmits an average of two more of these mutations to his child.

Studies in mice confirm that pups of older male mice harbor a relatively large number of mutations. And this hypothesis is consistent with the observation that a child with autism who has an older father tends to be the only child with autism in that family.

Other factors must contribute as well, however. Mathematical models of autism inheritance have indicated that de novo mutations account for about 20 percent of the increased odds of autism among children of older fathers.



## What else could explain these patterns?

It is possible that the connection runs the other way: Men who are likely to father a child with autism may have children relatively late in life. These men may have autism traits that delay their ability to find a partner.

Changes in chemical tags on sperm DNA as men age could also play a role. This hypothesis is consistent with epidemiological studies showing that the age of a grandparent at the time of a parent's birth can affect a grandchild's odds of having autism, and age alters chemical tags on sperm in mice. But this idea is controversial: There is no direct evidence that these tags are transmitted across generations in people.

Studies have noted additional factors, including elevated odds of autoimmune conditions in older parents. And because they are likely to be relatively wealthy compared with younger parents, older parents may be more likely to seek an evaluation for their child.

## How does a mother's age influence autism odds?

Overall, researchers have conducted fewer studies of maternal age and autism, and the results are not as clear-cut as they are for fathers. The effects of maternal age are more difficult to detect in epidemiological studies because women have children over a narrower age range than do men.

Some studies have suggested that a woman's chance of having a child with autism also increases steadily with age. The number of de novo mutations in egg cells increases with age, although to a lesser degree than it does in sperm. As with men, women who have autism traits may have children late. However, a comprehensive analysis found that for a woman over age 35, the chance of having a child with autism is lower than for younger women.

That study also suggested that women under age 25 are more likely to have a child with autism than older women. The finding echoed that of several other studies that reported that teenage mothers also have increased odds of having a child with autism.

## Does the trend toward having children later in life explain the increase in autism prevalence?

Probably not. Independent calculations suggest that the trend toward later parenthood accounts for only about 1 to 5 percent of the increase in autism prevalence. But investigating the link between parental age and autism could provide clues to the biology underlying the condition.







6 SEPTEMBER 2018

# The link between antidepressants and autism

by Jessica Wright





illustration by LAURÈNE BOGLIO

Among the many things a woman is supposed to avoid when pregnant are antidepressants, particularly a subtype of the drugs that some studies have linked to an increased risk of autism and attention deficit hyperactivity disorder.

Yet the evidence linking antidepressants to autism is thin. And untreated depression is dangerous for a mother and her child.

Here we explain what scientists know about the link between antidepressants and autism.



## Does taking antidepressants during pregnancy increase the odds that your child will have autism?

Maybe, but even if so, the risk is small. Several studies have looked at the health records of thousands of women for any boost in autism rates among the children of those who took antidepressants while pregnant. Some of these studies found up to a doubling of the odds of the women having a child with autism. However, because the initial risk of autism is small, this increase still adds up to a low absolute risk.

More importantly, women who take antidepressants may have other traits that are responsible for the increased rates of autism in their children. Many studies that control for these traits conclude that there is no risk from the antidepressants themselves.

## What are these other traits?

A history of depression or other psychiatric conditions in a woman is linked to increased autism risk in her children. And women with severe depression are more likely to continue to take antidepressants during pregnancy than those who are mildly affected, skewing any comparisons. Maternal stress, which can stem from severe depression, may also affect fetal development.

Two studies published last year looked at data from women who had taken antidepressants during one pregnancy but not

during another. In each study, siblings who were exposed to antidepressants in the womb turned out to have the same risk of autism as those who were not. These findings suggest that when we control for the mother's genetics or environment, antidepressants do not raise the risk of autism in her children.

Two other studies looked exclusively at women who have psychiatric conditions, only some of whom continued taking antidepressants while pregnant. One study showed no risk related to antidepressants when the researchers compared women with psychiatric conditions. The other study found that for every 100 children with an autism diagnosis, 2 might owe their diagnosis to antidepressant use in the mother while pregnant.

A woman's age, socioeconomic status, education level and residential locale (urban or rural area, for example) have all been shown to influence autism rates in her children. For example, in one study that showed a doubling of the odds with antidepressant use, the association disappeared when researchers controlled for 500 factors, including those mentioned above.

Women diagnosed with a medical condition might be particularly motivated to seek out an autism diagnosis for their child. This factor may be less of a concern in studies analyzing data from countries that have universal healthcare.





## What should you look for in a study linking antidepressants to autism?

The strongest studies are based on data from countries that have universal healthcare and maintain comprehensive databases of birth and medical records. These databases allow researchers to look for trends across hundreds of thousands of people. They track not only antidepressant use and autism diagnoses but also myriad other factors that may influence autism risk.

In general, it is important to check how many women were included in a study, and how many children have autism. If a study includes too few children with autism, its findings will not be statistically significant.

All studies should control for differences between women who take antidepressants during pregnancy and those who don't. The best studies will be designed specifically to address factors that may influence the analysis, such as those described above.

Some studies also look at the link between antidepressant use in men and autism in their children. These data give insight into the genetic link between depression and autism because a father's medication use cannot affect his child directly.

## What kind of study would prove that antidepressants are linked to autism?

Observational studies may never be able to provide conclusive results. In addition to the factors mentioned above, these studies lump together doses and types of antidepressants and may rely on unreliable self-reports of antidepressant use.

The only way to prove that an association exists would be to design a study in which one set of women take antidepressants and another a placebo. But such a study would be unethical because it would involve denying medication to a group of women who might need it. Animal studies can provide insights. However, it is difficult to document autism-like behaviors in an animal.

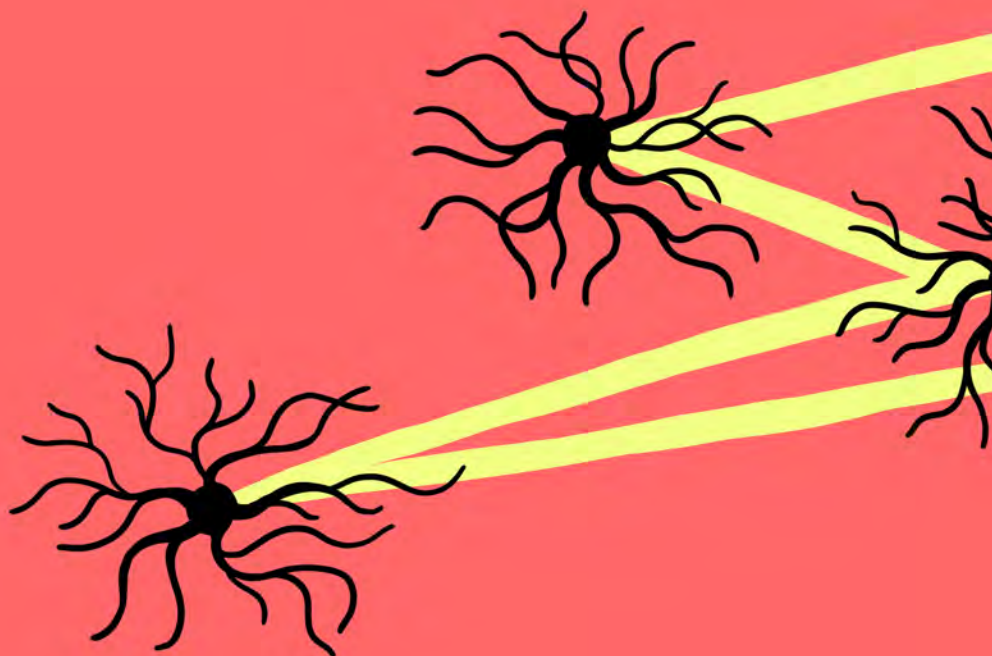
## So, what's the bottom line? Should women stop taking antidepressants while pregnant?

Women grappling with this question should consult their doctor. The risk of autism from taking antidepressants is small, if it exists at all. And severe depression during pregnancy or afterward can be harmful to both the mother and the child. But the risk-benefit analysis for the drugs will be different for each woman.



# **COMPETING THEORIES**





1 MAY 2019

# The signaling imbalance theory of autism

by Sarah DeWeerd



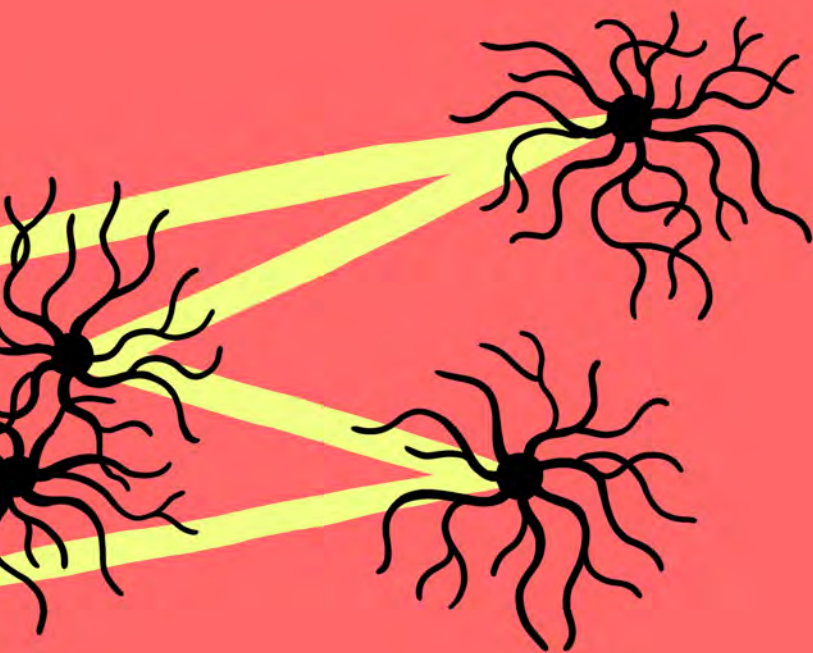


illustration by LAURÈNE BOGLIO

One of the most popular theories of autism's origins suggests that the condition arises from a hyper-excitable brain.

The autism brain may be overactive because of a 'signaling imbalance': too much excitatory signaling or too little inhibition. This may also explain why so many autistic people have seizures or epilepsy, which result from too much excitation.

The hypothesis has garnered a large following over the years. Here we explain its appeal, tempered by the naysayers.



## What is balanced brain signaling?

About 80 percent of neurons in the cerebral cortex, which covers the surface of the brain, transmit excitatory signals, primarily by releasing the neurotransmitter glutamate. The remaining 20 percent, known as interneurons, are inhibitory. They operate via gamma-aminobutyric acid (GABA).

The proper balance of these two types of signals enables brain cells to be active in some circumstances and muted in others. This underlies the brain's ability to take in sensory information, learn, remember and direct behavior.

## Why do scientists suspect a signaling imbalance in autism?

Many autistic people have epilepsy, which results from too much excitation in the brain. Recordings of brain activity during sleep show that many people with autism have unusually frequent spikes of activity.

Several mouse models of autism or related conditions also show signaling imbalances. Some have too few inhibitory neurons. Some children with autism seem to have low levels of GABA; postmortem brain studies also point to a shortage of GABA-related molecules in the brains of autistic people, suggesting reduced GABA signaling.

There is some genetic support for the theory, too. Many autism genes such as SHANK3 and NLGN1 are involved in excitatory signaling, and some in inhibitory signaling.

## How could a signaling imbalance lead to autism traits?

Too much activity in motor brain circuits could contribute to the repetitive behaviors and motor problems in autistic people; in circuits that process sensory information, it might cause hypersensitivity to sound, touch and other stimuli.

A signaling imbalance could also underlie social problems, but the link is less direct. Inhibitory signals are thought to tune neurons to respond only to certain cues; lack of inhibition could make it difficult for children to learn to interpret social cues.

## Do all experts subscribe to this theory?

No, some are clearly skeptical, saying the evidence to support it is scattershot and is difficult to compare across studies. Others note that there is no consensus on what the right signaling balance is, much less on what it looks like when it is off-kilter. The right balance of signals may vary from one person to the next and may depend on age and part of the brain.

There is some evidence that runs counter to the theory. For example, some studies hint at too much inhibition in autism: One study found an unusually high number of inhibitory neurons in postmortem autism brains, and another reported an unusually large proportion of GABA neurons among cells grown from autistic boys.



**THE AUTISM  
BRAIN MAY BE  
OVERACTIVE  
BECAUSE OF  
A ‘SIGNALING  
IMBALANCE.’**

However, some experts contend that that too much inhibition may also be a problem, or that this inhibition may reflect a compensation for the excess excitation.

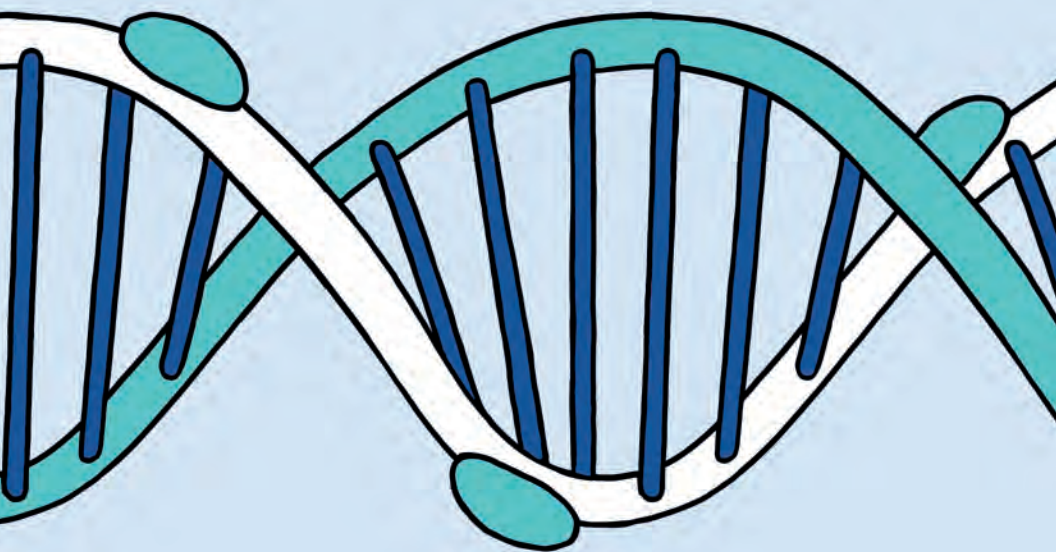
In January, researchers reported a signaling imbalance in four mouse models of autism, but said the imbalance does not lead to overactive neurons or circuits. Either the brain compensates for the imbalance or the imbalance is itself only a response to other problems; either way, it would not cause autism.

## How might the theory lead to autism treatments?

People with autism or related conditions may benefit from drugs that suppress excitation or boost inhibition. For example, an experimental drug called arbaclofen enhances inhibition and is in trials as a treatment for the condition. A study last year showed that a related drug, riluzole, boosts GABA levels in the brain in adult men with autism.

Researchers are also testing the theory by manipulating signals in mouse models and cultured neurons. They are using gene editing to decrease the expression of certain genes in subsets of neurons and trying to recapitulate the brain's balance of cells.





1 MAY 2019

# The multiple hits theory of autism

by Jessica Wright

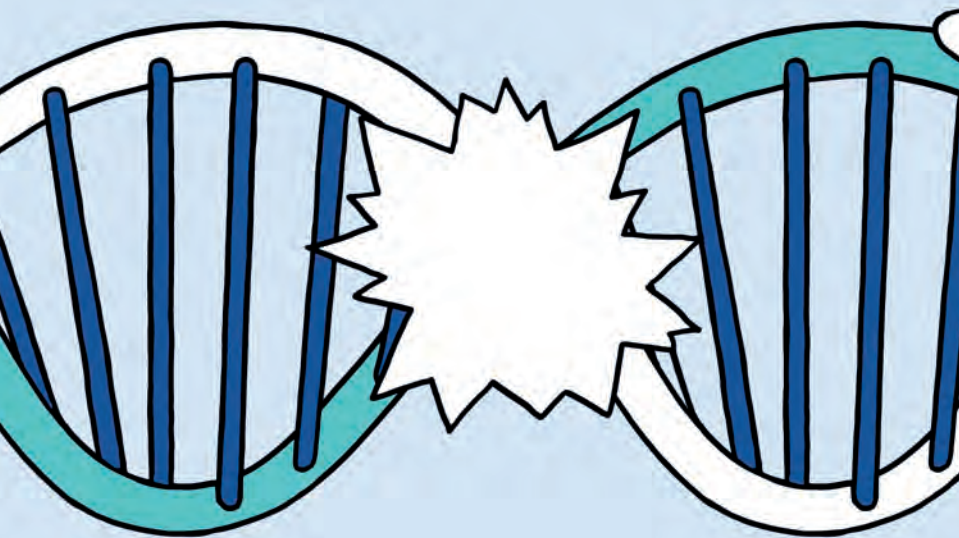


illustration by LAURÈNE BOGLIO

Over the past decade, researchers have looked for rare mutations found in people with autism but not in their neurotypical parents or siblings. This approach has yielded a list of roughly 100 ‘autism genes’ that harbor these powerful spontaneous mutations.

However, mutations in these genes are not guaranteed to cause autism. Even those who do have the condition vary significantly in the severity of their traits. Because these mutations are, by definition, not inherited, they also cannot explain why autism tends to run in families.

For these reasons, researchers are exploring the ‘multiple hits model,’ which posits that autism is often a result of combinations of mutations.



## What types of mutations can lead to autism?

There are three main types: rare spontaneous, rare inherited and common variants. These three types may all be at play in a single person with autism.

Rare, spontaneous (or de novo) mutations that are present in a person with autism but not in their families are the best known contributors to the condition. These mutations may be small—affecting a single gene—or may disrupt multiple genes. Rare inherited mutations tend to be less disruptive than de novo mutations, but can still be harmful.

Common variants are those present in more than 5 percent of the population. Each common variant has a mild biological effect, but in combination, they can determine complex traits such as height.

Each person in the population has a unique set of common variants that affects her autism risk. But studies show that common variants working together could account for as much as half of autism's genetic basis. Identifying the variants is difficult, however: Scientists know of only five with an autism link.

## What is the evidence for the multiple hits hypothesis?

Autism's diversity is the biggest argument in favor of this hypothesis: The same mutation can lead to a different set of traits in two people. For example, de novo mutations do not have the same effect on all carriers.



Only about 20 percent of people with a mutation in 16p11.2—among the strongest risk factors for autism—have the condition; all have some combination of other traits, such as developmental delay, obesity and language problems. Much of this variability depends on the rest of a person's genetic background.

In a large study last year, researchers uncovered a critical role for common variants in people with severe developmental delay or autism. These people are also likely to carry rare or de novo harmful mutations, suggesting that both types of mutations are involved in severe conditions.

Spontaneous and inherited mutations may also interact: People who have both a large spontaneous mutation linked to autism as well as a rare, inherited harmful mutation are more affected than those who carry only the former.

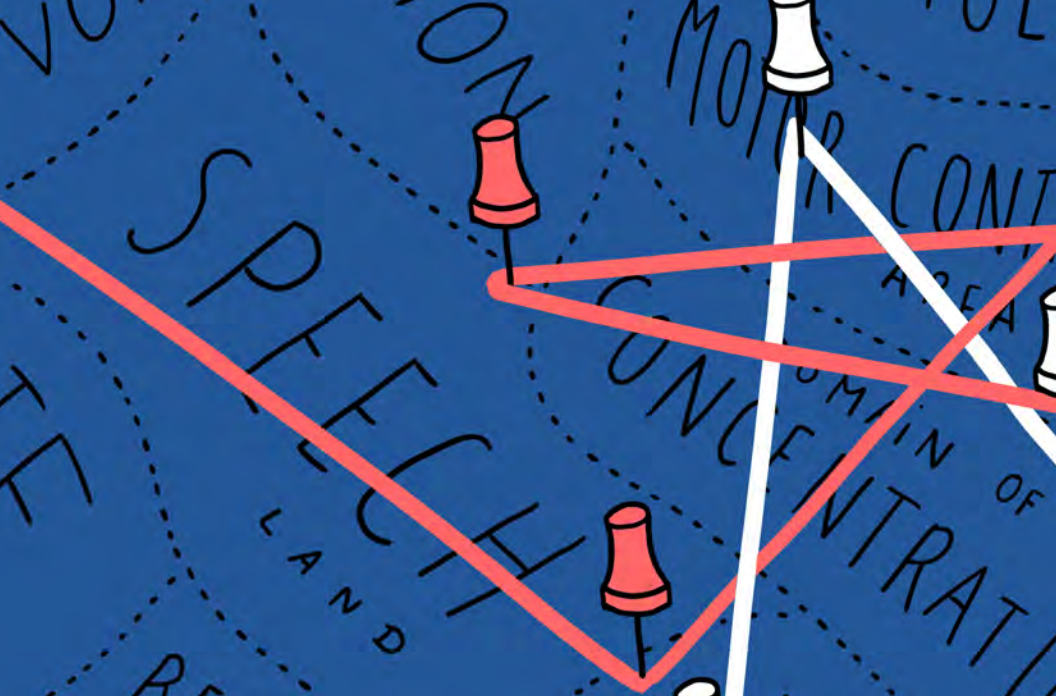
## What does the theory tell us about autism?

The theory may help explain why the same rare mutation only sometimes leads to autism and in other cases, leads to epilepsy, schizophrenia or other conditions. The common variants a person has may determine whether a rare mutation leads to autism or to something else.

It may also explain why a de novo or rare autism mutation varies in its impact: Second hits may serve as buffers. To investigate this idea, researchers are sequencing the genomes of unaffected parents or siblings to identify protective variants.

One way a second hit could buffer—or enhance—the effect of a first hit is by altering gene expression. Most mutations associated with autism affect only one copy of a gene. If a second hit boosts expression of the functional copy, it may counteract the effect of the mutation.





1 MAY 2019

# The connectivity theory of autism

by Rachel Zamzow

On the face of it, the ‘connectivity theory’ of autism is simple: In autism brains, the theory goes, communication between regions is atypical. But exactly how is complex—and unclear.

By connectivity, researchers generally mean ‘functional connectivity’—a measure of the degree of synchronized activity between different brain regions.

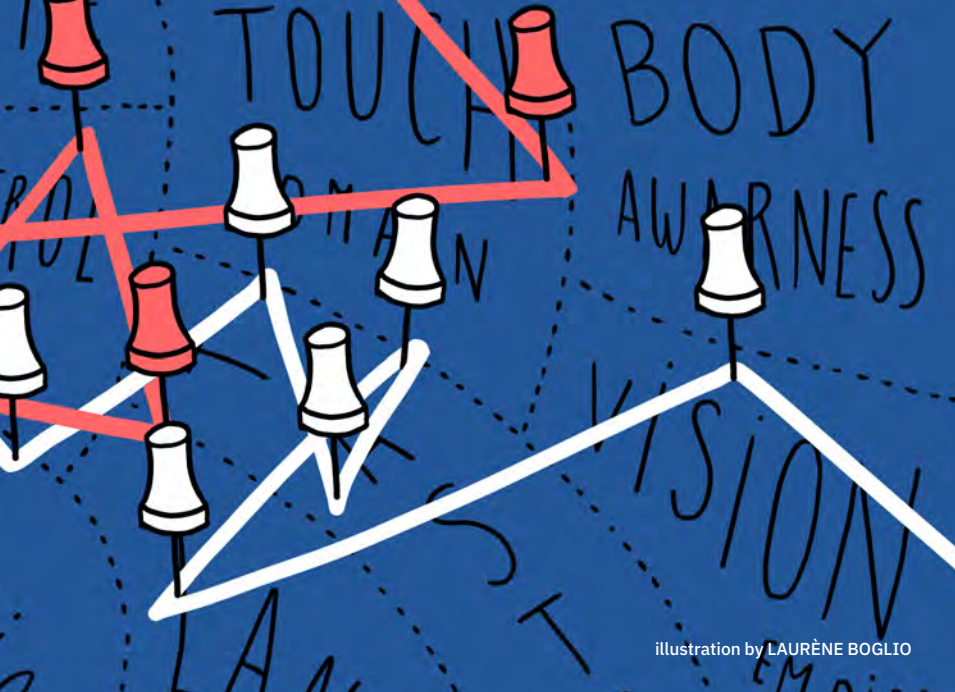


illustration by LAURÈNE BOGLIO

Over the past decade or so, a growing number of autism studies have examined connectivity patterns while participants rest in a brain scanner. Some of this work indicates that autism is characterized by underconnectivity between distant brain regions and overconnectivity between neighboring ones; others show differences in connectivity within certain brain networks. In one study, connections within the default mode, or ‘daydreaming,’ network of autism brains looked especially weak.

Out of these disparate findings, researchers have constructed the broad-strokes connectivity theory. But the results of some studies are at odds with the proposed patterns, and some find no differences between autism and control brains at all. As studies become bigger and more sophisticated, the number of divergent findings grows.

Here we explain these conflicting results and how researchers are addressing them.



## Why are connectivity findings in autism so inconsistent?

One of the main reasons is autism's diversity: Each person with autism is different from the next, with a unique constellation of behaviors, experiences and genetics. It's no wonder individual connectivity patterns also differ.

So some researchers have started to look for connectivity patterns in subgroups of people with the condition. For example, mutations in the autism-linked genes MET and CNTNAP2 produce patterns that differ from those in people without these mutations. Connectivity may also differ between men and women with autism.

Large datasets, including the Autism Brain Imaging Data Exchange, may help researchers pinpoint clusters of autistic individuals with distinct connectivity patterns. Some researchers have started searching for clusters on a smaller scale, with a focus on regions of the brain that govern language, for example.

## What other factors affect connectivity patterns in the brain?

Age. Several reports suggest that connectivity differs between children and adults with autism. For example, autistic children may have unusually strong connections in several brain

networks; autistic adults tend to show weaker connections in some of the same networks. Homing in on puberty might reveal why their brains appear to switch in this way.

Researchers could also gain insight from studying autistic toddlers before they receive treatment. A study of sleeping 2- to 4-year-olds suggests that connections between some brain regions are unusually weak, not strong, in young children with autism.

The most valuable data come from studies that track connectivity in the same people over time. One of the few studies of this type suggests that connectivity between some brain networks increases from early to late adolescence in typical people but remains stable in autistic individuals. Several studies following children through adolescence are likely to provide more information.

## Can research methods influence connectivity results?

Yes. Results from brain imaging studies are subject to variations in magnet strength, experimental approach and methods of data analysis. Connectivity between some brain regions is stronger, for example, when participants' eyes are open than when they are closed. Psychotropic drugs, such as fluoxetine (Prozac) or methylphenidate (Ritalin), can also alter patterns.

Head movement and other motion, such as breathing, can distort results as well. Researchers are still ironing out ways to minimize or correct for these factors. Using various imaging techniques in combination may provide richer data and more



**EACH  
PERSON  
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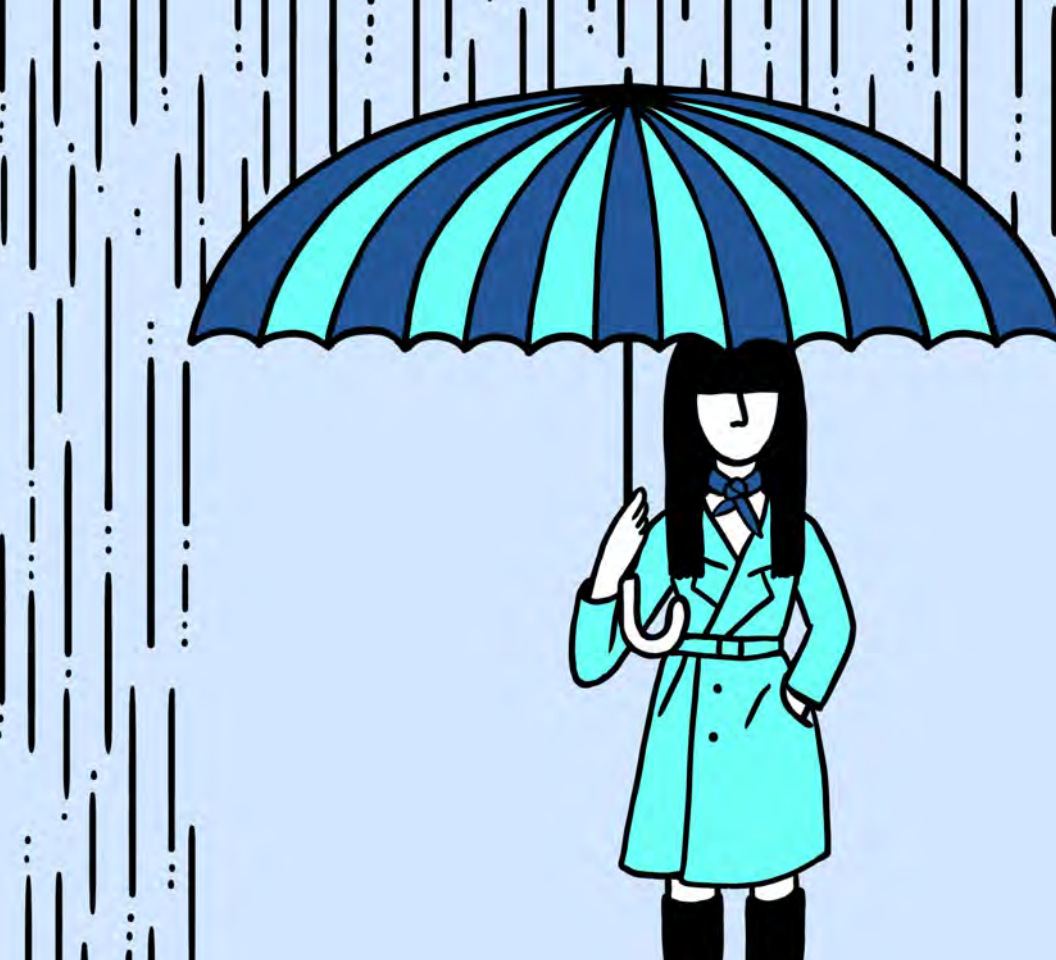
reliable findings, some say. The most common method is functional magnetic resonance imaging. Other methods include magnetoencephalography, which tracks fluctuations in the brain's magnetic fields, and diffusion tensor imaging, which maps structural connections.

## Could connectivity serve as a biomarker for autism?

It's unlikely. Some scientists are searching for biological markers that reliably signal the condition, but it has been hard to show consistent differences in connectivity. Patterns of connectivity in autism also may overlap with those of other conditions, such as schizophrenia or depression.

Part of the problem lies in researchers' uncertainty about how to analyze scans. A method called machine learning is often used to classify participants as autistic based on their connectivity, but different algorithms can produce discrepant findings. And researchers frequently cannot replicate their findings when they apply their methods to a new set of data.





1 MAY 2019

# The female protective effect

by Hannah Furfaro





illustration by LAURÈNE BOGLIO

One of autism's most persistent puzzles is why four times as many boys are diagnosed with the condition as girls.

Diagnostic bias partly explains this ratio. A leading theory of autism, the 'female protective effect,' also offers a powerful explanation. The theory suggests that girls and women are biologically shielded from autism.

Here we explain the theory and step through the data that support or undermine it.



## What are the origins of the female protective effect theory?

In the 1980s, Luke Tsai, then at the University of Michigan in Ann Arbor, found that autistic girls have more relatives with autism or certain language impairments, on average, than do boys with the condition. This finding hints that girls need to inherit more factors related to autism than boys do to show traits of the condition. Several large studies since then have supported Tsai's observation.

## What evidence supports this theory?

The most compelling evidence for the theory comes from several large studies of families or twins. One study found that the younger siblings of autistic girls are more likely to also have the condition than are the younger siblings of autistic boys. Other studies suggest that girls are more resistant to mutations linked to autism than boys are—that is, girls may carry the same mutations as autistic boys and yet not have the condition.

Some studies suggest that more mutations, or 'hits,' are required to trigger autism in girls than in boys. A 2011 study showed that autistic girls have more spontaneous DNA duplications or deletions, called copy number variations (CNVs),


than autistic boys do; another study confirmed the finding three years later. This study also reported that autistic girls are three times as likely as boys to carry CNVs that include autism genes.

Some animal experiments also support the theory. Female mice with a deletion in the 16p11.2 chromosomal region, which is linked to autism, do not have the learning problems that males with the deletion do; they appear to compensate for the loss through a protein called ERK. Another team found that females in a different mouse strain that have the 16p11.2 deletion compensate behaviorally.

## Could diagnostic bias, rather than this protective effect, explain autism's sex ratio?

Yes. Autism manifests differently in girls than it does in boys. But the tools used to diagnose and screen for autism are based primarily on data from boys. They often do not account for variation in autism characteristics across sexes. As a result, many autistic women and girls are diagnosed with the condition late or not at all. This underdiagnosis may have led to a skewed sex ratio.





## Is there evidence contradicting the female protective effect?

Yes, but not much.

If autistic girls carry more familial risk factors than autistic boys, the siblings of autistic girls should also be at a heightened risk for autism or autism traits. But some scientists have found the opposite.

A 2015 study found no association between the sex of autistic children and the extent of autism traits in their younger siblings. However, a 2013 study showed that siblings of autistic girls have more autism traits than do siblings of autistic boys. Overall, there is more support for the theory than against it.

# Why is it important to study this effect?

Characterizing the factors that protect girls from autism could help researchers develop targeted treatments or lower the risks associated with the condition.

But pinning down a biological explanation for the female protective effect must come first. So far, all the evidence in support of the theory is indirect. Ideally, scientists would identify specific aspects of molecular pathways in girls that underlie their resistance to autism.

One team is studying sex differences in the brains of autistic individuals; another is searching the genomes of large numbers of girls for genetic variants that might explain the protective effect.



PARENTS

ENVIRONMENTAL RISKS

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EARLY INTERVENTION

SEX RATIO

GENETICS







1 MAY 2019

# The extreme male brain

by Hannah Furfaro





illustration by LAURÈNE BOGLIO

The ‘extreme male brain’ theory posits that people with autism process the world through a ‘male’ lens and take an interest in stereotypically male topics, such as how machines work or weather patterns. And they may have trouble with tasks that women are supposedly better at, such as grasping social cues.

Over the years, the theory has garnered support—and derision—from autism researchers. Here’s everything you need to know about how the extreme male brain theory came to exist, the evidence that backs it and the controversy surrounding it.



## What is the extreme male brain theory?

The theory is based on the idea that men and women differ in fundamental ways, and that the differences lie along a continuum. Subscribers to the theory assign the term ‘empathy’ to the female end of the continuum, referring to a constellation of social skills, such as the ability to intuit others’ emotional states.

At the male end is the tendency to ‘systemize,’ or to recognize patterns and understand natural and technical systems, such as the weather or a computer.

The theory broadly proposes that autistic people, no matter their sex, tend to be at the systemizing end of the continuum—that is, they have an ‘extreme male brain.’

## What are the theory’s origins?

In the mid-1990s, British researcher Simon Baron-Cohen incorporated tests of social intelligence and pattern recognition into his autism studies. In the general population, these tests show sex differences: Women tend to perform well on the tests of social intelligence, whereas men tend to excel at following rules and recognizing patterns. Baron-Cohen found that autistic people generally have trouble with the former but do well with the latter.

In 2002, he proposed the extreme male brain theory of autism to account for these findings. He and his colleagues then developed a pair of self-report questionnaires to measure systemizing abilities.

## What evidence backs the theory?

Last year, Baron-Cohen's team analyzed responses to these questionnaires from 600,000 people, including 36,874 with autism. The results suggest that autistic men and women both tend toward systemizing.

Baron-Cohen's other work hints at where this tendency may originate. Some people with autism may have been exposed to elevated levels of sex steroid hormones, such as testosterone, in utero, he says. Excess testosterone may alter the structure of the developing brain in ways that affect thinking patterns. But studies from other labs question the link between excess testosterone and autism.

Brain-imaging studies have revealed anatomical patterns in male and female brains consistent with the extreme male brain theory—but the data are not uniformly supportive. In one small study, researchers showed that the brains of autistic men and women are structurally more similar than those of typical men and women. Another study also showed support for the theory in some brain networks. However, in March, researchers retracted a large 2017 study that had affirmed the theory because of a major error in the analysis.





## What are some criticisms of the theory?

Some experts question the theory's fundamental assumption—that measurable differences exist between men and women in abilities such as social communication. If any do exist, they are likely to be small, says David Skuse, professor of behavioral and brain sciences at University College London.

Another criticism is that, for years, the questionnaires used to test the theory included too many questions on 'male' topics, such as reading about or working on machines. The tests have since been revised, but their questions are still based on gender stereotypes or, at least, an overly simplistic concept of sex differences, experts say. And some of these differences may not be relevant to autism traits.

“The explanations to date are based on really gross misinterpretations of developmental data of typical kids and fairly shaky biological data,” says Catherine Lord, distinguished professor in residence of psychiatry and education at the University of California, Los Angeles. Most of the support for the theory comes from the work of Baron-Cohen or his former students, others say. “There's still a relative lack of independent replication,” says Meng-Chuan Lai, assistant professor of psychiatry at the University of Toronto in Canada, who completed his doctoral and postdoctoral work in Baron-Cohen's research center.

## What are some misconceptions about the theory?

Most of the misunderstandings arise from the theory's name. It does not suggest that all autistic women think like men or that autism is tied to other 'male' features, such as large body size. Baron-Cohen says the theory only pertains to two categories of cognition: systemizing and the ability to intuit others' emotions.



1 MAY 2019

# The predictive coding theory of autism

by George Musser



illustration by LAURÈNE BOGLIO

The predictive coding theory holds that our experience of the world comes from within. Our brains generate a model of the world that predicts what we are going to see, hear, touch, smell and taste. The job of our senses is to check our predictions to make sure our inner model does not drift far from reality.

The theory is also called predictive processing or the ‘Bayesian brain,’ in a nod to its mathematical underpinnings.

Supporters of the theory apply it not just to perception, but also to emotions, cognition and motor control. So, we move our arm because we predict we will move it, and the body makes the prediction come true.

The predictive coding theory of autism proposes that an autistic person’s brain does not form accurate predictions or that sensory



input overrides these internal predictive models. As a result, the autistic person is overly sensitive to external input and unable to tune it out. They find it hard to process social cues and communication in time to generate an appropriate response because their internal models of how people behave are not well formed.

In this way, predictive coding could account for the social, sensory and other difficulties of autism.

Here we flesh out this theory and describe the data supporting it.



## How does the theory apply to autism?

Predictive coding frames autism as a difference in the brain's learning curve—where learning covers everything from making sense of a complex visual scene to cramming for a history test.

According to the theory, a parameter known as 'precision' determines the weight the brain gives to discrepancies between sensory input and our expectations. When we learn something new, the brain dials up the precision and uses the input to form a model. When the brain judges that the model is complete, it dials down the precision, assuming that any further discrepancies are random variations that it can safely ignore.

The modeling is hierarchical. In the visual system, for example, it starts with geometric details and builds up to global features and abstractions.

Biologically, the brain adjusts precision by shifting its proportions of chemical messengers such as glutamate, dopamine and norepinephrine. Subjectively, we feel surprise, then the satisfaction of mastery, and finally boredom.

In autism, so the idea goes, the brain is slower to recal-



brate precision. It remains attuned to details but finds it harder to generalize. The theory could explain why autistic people describe feeling frequently overstimulated and perpetually surprised, why they prefer routine and why they may have trouble reading other people.

## What's the experimental support?

In both daily life and lab experiments, autistic people are slow to tune out background noise and quick to pick up on novelty in their environment. It's as if they are less bound by prior expectations. Measurements of brain and skin responses to sensory information show that they do not readily habituate to metronomes or other repeated stimuli. They are also less able to perceive optical and multisensory illusions that play off expectations.

One experiment uses a learning task to study how the autistic brain interprets changing patterns. Researchers play a high or low beep, show a picture of a face or house, and ask participants to press the 'face' or 'house' button. At first, a high tone presages a house, but later a low tone does. The relationship is never perfect—just higher odds for one tone or the other—and so it is not obvious whether a break in the pattern marks an exception or a new rule.

Autistic people are slower at the task overall, but faster to notice when the pattern has changed, suggesting that they anticipate change—as opposed to clinging to a pattern—more than typical people do.

It's not clear whether their predictive difficulty is in forming expectations or in senses that override those expectations. Experiments seem to favor the second option.



## So it's a done deal, then?

By no means. In some studies, autistic people handle predictive tasks—habituating to repeated stimuli, responding to some kinds of illusions and discerning patterns unfolding over time—as readily as neurotypical people do. What's more, the direction of causation is not clear: Instead of problems with prediction throwing a wrench into a person's social cognition, it may be that social difficulties alter the development of a person's internal models.

## How does predictive coding relate to other theories for autism?

Predictive coding overlaps with other hypotheses of autism. Like some of these others, it suggests that in people with autism, the brain focuses too heavily on details and is slower to zoom out to see the big picture. It also suggests that the autism brain has difficulty divining other people's intentions as an example of struggling to make predictions in general; this idea is consistent with the theory that autistic people struggle with 'theory of mind.'

## Does predictive coding offer insights into other conditions?

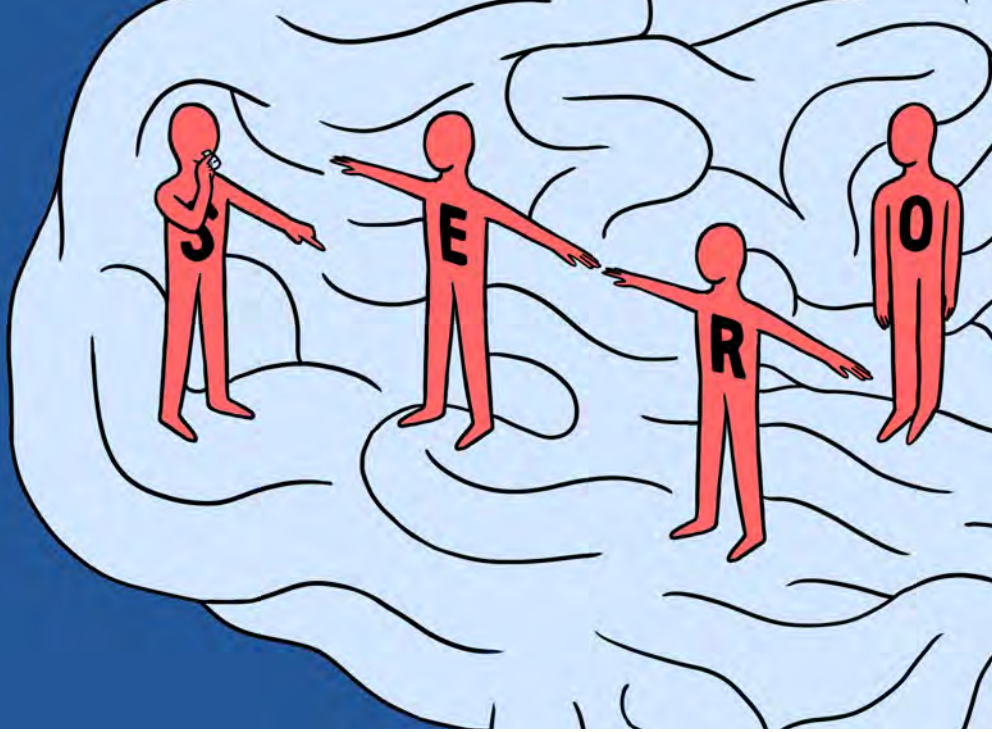
Predictive coding may help to make sense of the connections between autism and other conditions, most notably schizophrenia. If the brain in autism gives too much weight to sensory input, the brain in schizophrenia might give it too little, conferring too much sway to internal expectations and loosening the tether to external reality. That bias might explain the hallucinations in schizophrenia. In other ways, though, autism and schizophrenia are similar. Both may involve delusions, which are false beliefs as opposed to false perceptions. Predictive coding suggests that delusions may occur when expectations are too weak and the brain overcorrects, causing a person to draw grand conclusions from slender evidence.

Autistic people may also experience higher rates of Parkinson's disease. In people with this condition, problems adjusting 'precision' cause the brain to prematurely decide that a physical movement is complete. This leads to motor rigidity.

## What does this predictive coding model of autism mean in practical terms?

If the autistic brain is juggling sensory input and expectation differently, people with the condition might be able to learn to compensate. For instance, coaching could help them learn to shift their focus from low-level details to higher-level ones.





1 MAY 2019

# Serotonin's link to autism

by Nicholette Zeliadt

Serotonin, the brain chemical best known for its link to depression, may also be involved in autism.

Serotonin has many roles throughout the body, including in mood, sleep, appetite and sociability. In the intestines, it stimulates muscles involved in digestion; in the blood, it causes vessels to shrink or expand; and in the brain, it relays messages between neurons. Its



illustration by LAURÈNE BOGLIO

levels in the brain are closely tied to depression. Many antidepressants work by increasing the levels of serotonin at neuronal junctions.

Tenuous ties between serotonin and autism first surfaced decades ago. In 1961, a study of 23 autistic people reported that 6 of them had an unusually high level of serotonin in their blood. Since then, researchers have consistently found that about one in four people on the spectrum has high blood serotonin.

That result is “incredibly well replicated,” says Jeremy Veenstra-VanderWeele, professor of psychiatry at Columbia University.

Motivated in part by these results, several research teams have tested antidepressants as a treatment for autism over the past 20 years—with mixed results. Interest in serotonin’s role in autism has grown in the past five years, due in part to mouse studies that implicate the chemical in social behavior.

Here’s what we know so far about serotonin’s role in autism.



## What could explain the high serotonin levels in the blood of people with autism?

Blood serotonin levels are controlled in part by a protein called the serotonin transporter, which moves serotonin from the gut, where most serotonin is made, into certain blood cells.

These levels are highly heritable, suggesting that genetic factors control them. Some people with autism may carry variants in the serotonin transporter that enhance its ability to move serotonin into blood cells. Mice with these variants have unusually high blood levels of serotonin and behaviors reminiscent of autism.

## What does serotonin do in the brain?

In the fetus, serotonin helps neurons form and travel to their correct locations; it also helps them link to other neurons at junctions called synapses. Too much or too little serotonin can be harmful: Mice exposed to too much in utero show altered development in a brain region that responds to whisker movements; those with too little have repetitive behaviors and social difficulties.

In the mature brain, serotonin is a neurotransmitter: It relays messages between neurons. Its level at the synapse is tightly controlled by the serotonin transporter, which pumps serotonin back into neurons and recycles it for later use. This transporter may be altered in people with autism.

## What do blood levels of serotonin have to do with serotonin in the brain?

It is unclear, because serotonin in the blood cannot pass into the brain; the brain makes its own. Genetic variants that turbocharge the transport of serotonin into blood cells are predicted to have the same effect in neurons, effectively leaving less of it available to relay messages across synapses. Antidepressants might be able to help by restoring levels of serotonin at the synapse. How does the brain's serotonin level relate to autism?

Some studies point to low serotonin levels in the brains of autistic people. When autistic adults adopt a diet low in the amino acid tryptophan—the raw material for serotonin—their repetitive behaviors worsen and their irritability increases. They also show altered patterns of brain activity in regions involved in face processing, suggesting that serotonin influences social behavior. Brain-imaging studies also hint that some autistic children make too little serotonin in the brain, and in others, too little serotonin binds to its receptors.





## Can treatments that increase serotonin levels ease autism traits?

Possibly. Antidepressants that allow serotonin to remain at the synapse for longer seem to ease repetitive behaviors in some autistic adults. These drugs, called selective serotonin reuptake inhibitors (SSRIs), have not yet been shown to benefit children with autism. But clinical trials of these drugs are hampered by powerful placebo effects that might make it hard to tease out the benefit.

Preliminary evidence suggests that in adults with autism, the active ingredient in the drug ‘ecstasy,’ which raises serotonin levels in the brain, seems to ease social anxiety.

Some mouse models of autism have low brain serotonin levels. Treating one such strain of mice with an SSRI starting at birth prevents autism-like social behaviors. And artificially boosting serotonin in in another mouse model makes the mice more social.



## Do serotonin levels in utero affect a child's autism risk?

Some studies have explored whether exposure to antidepressants in utero has any effect on autism risk. The answer is unclear. One problem is that researchers are often not able to separate the effect of the antidepressant from that of the mother's underlying depression. Simply having a family history of depression, for example, is associated with autism.

## Where is research on serotonin and autism headed?

Some researchers are testing whether drugs that activate serotonin receptors make mouse models of autism more sociable. Others are working on strategies that dampen the activity of the serotonin transporter without blocking it completely.



**TESTS,  
TRAITS AND  
INTERVENTIONS**

3



5 NOVEMBER 2018

# Autism diagnosis

by Hannah Furfaro



illustration by LAURÈNE BOGLIO

Clinicians diagnose autism using behavioral tests for the core features of the condition: communication difficulties, social challenges and restricted or repetitive behaviors.

But getting an autism diagnosis can be a long and challenging process. Because autism is a heterogeneous condition defined by behavior and not by a single gene, blood or brain profile, clinicians use reliable diagnostic tools to assess an individual's strengths or weaknesses and develop personalized treatment plans.

However, clinicians in a given area may lack the expertise or



resources needed to implement these standardized diagnostic tools. And families seeking diagnosis may face a long wait.

Some scientists are working to improve the available screening and diagnostic instruments and people's access to them. They are also developing new diagnostic tools.

## What are the standard tools for screening and diagnosing autism?

Clinicians use a range of tests to diagnose autism. Screens flag people at risk for the condition, and diagnostic tools then help clinicians determine whether a person is autistic.

The Modified Checklist for Autism in Toddlers (M-CHAT), developed in the early 1990s, is the preferred screening tool and is widely used in the United States. Parents answer 23 'yes-no' questions about their child's social, motor and language skills at the child's 18- and 24-month checkups. A revised version of the screen includes fewer questions and a follow-up interview between the child's caregiver and the pediatrician. Other screens, such as the Gilliam Autism Rating Scale, are used primarily in school settings and help flag children older than age 2.

To diagnose the children these screens flag, clinicians typically use a pair of standardized behavioral tests: the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). Clinicians using the ADOS observe children's behavior and how they engage in social situations for up to an hour. The ADI-R is a 93-item questionnaire that caregivers complete over several hours. Clinicians

sometimes also incorporate other tools that evaluate autism traits. For instance, they use the Vineland Adaptive Behavior Scales to assess daily-living skills and the Social Responsiveness Scale to identify problems with social skills.

## Which tests are the most reliable?

The ADOS and ADI-R identify the greatest proportion of autistic people and make the fewest false identifications. The ADI-R has been translated into more than two dozen languages and is the preferred test among clinicians in many countries.

The M-CHAT is quick and can be widely administered, but as a screen, it only provides an indication of risk and is not always accurate. Still, versions of the M-CHAT are used in the U.S., the United Kingdom and several other countries. Researchers in China are testing a modified version of the M-CHAT as a screening tool for that country. And the revised M-CHAT with the follow-up interview is more reliable than the original questionnaire.

## Which aspects of the tests are most in need of improvement?

Scientists developed diagnostic tests for autism largely using data from boys, so the tests are not as good at detecting autism in girls. Autism is also underdiagnosed among minorities



and children from low-income families, although it's unclear whether existing diagnostic tools contribute to the disparity.

Some tools work better at certain ages than at other ages. For instance, three 2017 studies indicate that the M-CHAT is more accurate when conducted at 24 months of age than at 18 months—and wrongly flags others as having autism. One study showed that only 36 percent of children in this age group whom the revised M-CHAT flags for autism actually have the condition.

## What other factors hinder autism diagnosis?

Autism can be diagnosed by age 2, but early screening isn't universal, and some children aren't flagged until they begin preschool—or even much later.

One of the biggest barriers to early diagnosis is a dearth of trained clinicians. Doctors need significant clinical expertise to administer the ADOS and the ADI-R, so many forego these instruments in favor of shorter, less rigorous tests. What's more, pursuing a diagnosis can also be costly and time-intensive for families that live far from an expert clinician.



## What new tools are on the horizon?

Many teams are looking for biomarkers of autism—objective biological signatures of the condition. Some are using eye-tracking technology to assess what autistic people pay attention to; several studies show that autistic people tend to avoid others' eyes, preferring instead to look at their mouths or at scenery. Eye-tracking can even reveal telltale patterns of focus in infants, but it is still a long way from being ready for use in the clinic. Heart rate, sleep patterns and body movements may serve as biomarkers, too.

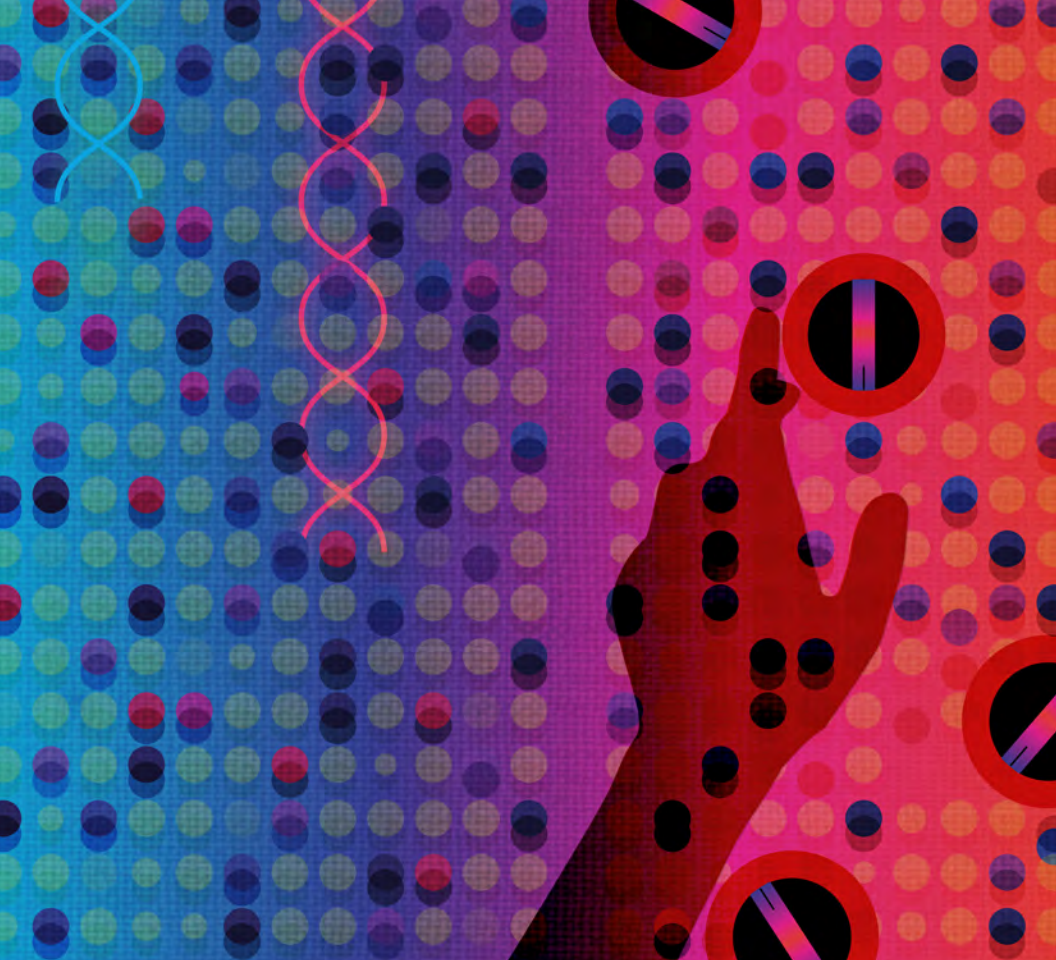
And researchers are looking for brain signatures of autism by using technologies such as magnetic resonance imaging. Machine-learning tools may aid in the analysis of these biomarkers. Genetic testing could also inform diagnosis: A long list of genes is implicated in autism.

Some of these tools face practical barriers. Broad clinical use of brain scanning is prohibitively expensive, for example, and genetic testing can be costly for families when it isn't covered by insurance.

Meanwhile, some teams are developing behavioral screens that identify autism in infants; others have found ways to reach parents in the U.S. with limited English skills.

The next phase of behavioral instruments may characterize a person's autistic features enough to identify subtypes of autism—and develop targeted treatments based on these profiles.





10 APRIL 2019

# Clinical genetics

by Jessica Wright



illustration by CHAD HAGEN

Autism is primarily a genetic condition: Most of the risk for autism comes from genes. Mutations in more than 100 genes are known to lead to the condition.

There are four types of tests that can detect these mutations, as well as structural variations that may lead to autism. As researchers learn more about the genetics of autism, the tests have become more informative: More of the mutations they find have ties to autism and to known health consequences. Here's a primer on how genetic tests work, their value for autism and what to expect from the results.



## Is there a genetic test for autism?

No. A genetic test cannot diagnose or detect autism. That's because myriad genes along with environmental factors may underlie the condition. Roughly 100 genes have clear ties to autism, but no single gene leads to autism every time it is mutated.

For example, only about one in four people missing a stretch of chromosome 16 called 16p11.2 has autism. This and other mutations are also associated with other conditions, such as epilepsy or intellectual disability.

## Why would an autistic person get a genetic test?

If a test reveals a harmful mutation with known ties to autism, the result could give the autistic person and her family an explanation for the condition. Some families also find emotional and practical support from others dealing with the same mutation. There are no drugs tailored to particular autism mutations. But the mutations are often linked to other health problems, such as epilepsy, kidney problems or obesity, so having the information could help prevent or treat those problems.

# What types of genetic tests are available?

There are four main types of tests. The oldest is karyotyping, the inspection of chromosomes under a microscope. This test reliably detects changes to segments larger than 10 million base pairs. A test called chromosomal microarray analysis identifies duplications or deletions of DNA too small to show up on a karyotype. Still, a karyotype is necessary to identify instances in which chromosomes evenly trade a chunk of genetic material.

To detect even smaller duplications or deletions, and single base-pair swaps, clinicians must sequence or scan for mutations across single genes. Some clinicians use commercial autism tests that sequence a predetermined set of genes, but these panels often do not include top autism genes.

An alternative is to sequence all of a person's protein-coding DNA, or the exome. Clinicians may sequence the exomes of both parents as well as the child to find mutations present in only the child. These spontaneous mutations are more likely to contribute to autism than are inherited ones. Exome sequencing is expensive, however, and often not covered by insurance.

Sequencing the entire genome is the most thorough method. It reveals mutations in any part of a person's genome, not just the 1 percent that includes genes. It is still only a research tool, but as its price falls and it becomes more widely available, it could replace the other tests.



For now, American medical academies recommend only karyotyping or chromosomal microarray analysis for autism. They also advise looking for point mutations in FMR1, MECP2 or PTEN, but only when a child shows other signs of the syndromes associated with mutations in these genes.



## What proportion of autistic people find answers from genetic tests?

Relatively few. Karyotyping finds a relevant mutation in 3 percent of autistic people, and microarray analysis in 10 percent. Sequencing the three genes associated with syndromes could identify an autism mutation in 14 percent of autistic people.

Combining these methods with sequencing the exome could yield results in as much as 40 percent of people with autism.

In one 2015 study, microarrays found mutations that could explain autism in 9 percent of children with the condition. Sequencing exomes revealed mutations in another 8 percent.

The likelihood of finding a known genetic variant increases if the autistic person also has intellectual disability, seizures or unusual facial features.

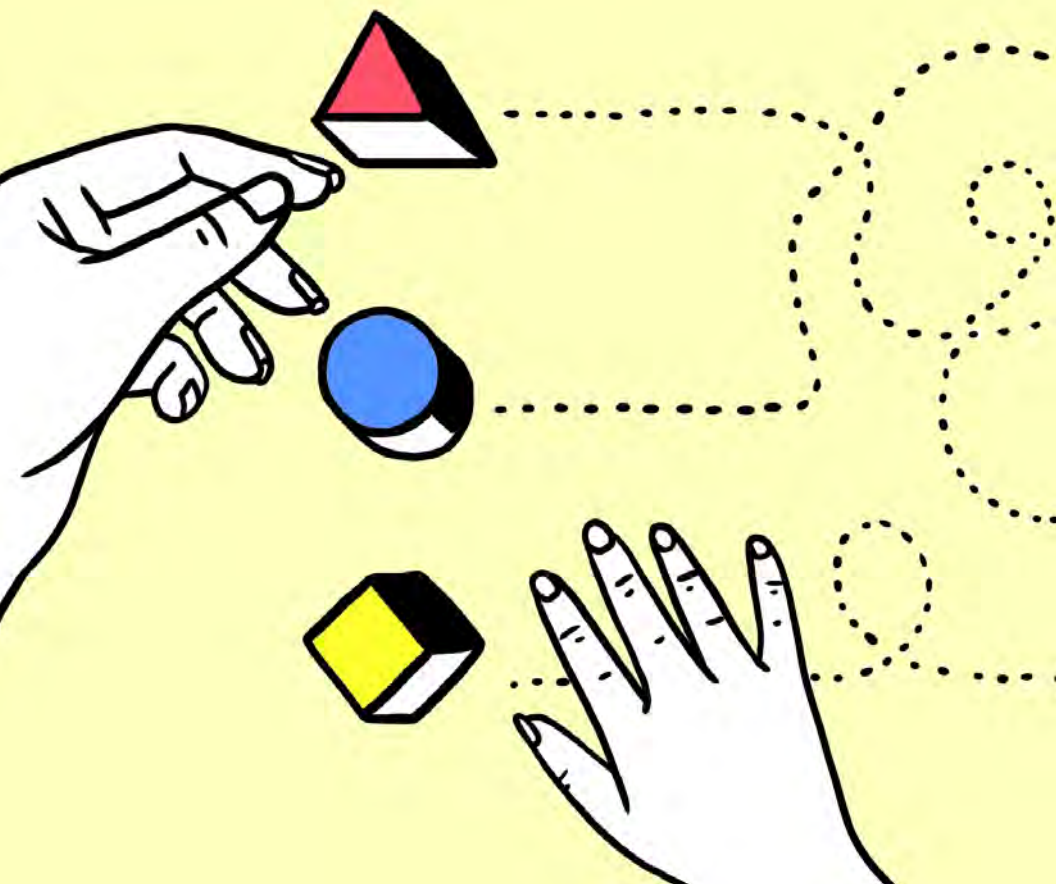
## What if a genetic test turns up nothing?

A negative result does not mean the person does not have a mutation that can cause autism. The test in question might not pick up that particular mutation, or perhaps the mutation does not yet have a known connection to autism.

Many of the genes linked to autism today were not associated with the condition five years ago. Most genetic testing facilities reanalyze results once a year based on the latest findings.







4 OCTOBER 2018

# Early interventions

by Jen Monnier



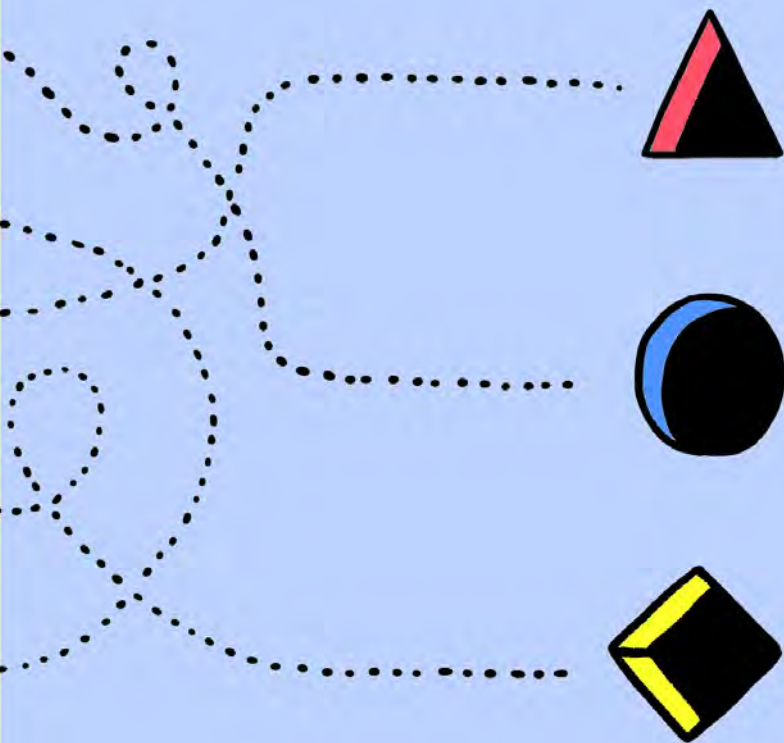


illustration by LAURÈNE BOGLIO

In 1987, psychologist Ole Ivar Lovaas reported that he had created a therapy that would make the behavior of some autistic children indistinguishable from that of typical children by 7 years of age. His approach, applied behavioral analysis (ABA), involves hours of drills each day, in which children are rewarded for certain behaviors and discouraged from others.

But Lovaas had overstated his case: Of the 19 children in his study who were treated, only 9 went on to meet typical developmental milestones.



Still, given the dearth of treatments for autism, ABA quickly became popular and is now the most common behavioral therapy for autism—but it is not without controversy. ABA also forms the basis for most interventions delivered early in childhood. The accepted wisdom in autism research holds that early intervention offers the best promise for an autistic child’s well-being. But how effective are these therapies?

Here’s what researchers know about early intervention.

## What are the main types of early intervention?

ABA is the most popular of the therapies offered early in childhood. ABA now refers to a broad group of therapies that use reward to encourage and reinforce a set of skills.

One such treatment, the Early Start Denver Model (ESDM), applies the techniques of ABA during play to help a child express feelings, form relationships and speak. By facilitating positive interactions, the therapy is designed to help the child build social-emotional skills alongside cognition and language.

Another leading intervention based on ABA, called pivotal response treatment (PRT), is also applied during play. It targets pivotal areas of development, such as motivation and self-management, rather than specific skills. This approach teaches a child how to respond to verbal cues. For instance, when a child requests a toy, the therapist or parent asks the child to name the toy; the child gets the toy once she complies.

Other treatments based on ABA target specific skills. For example, a therapy called Joint Attention, Symbolic Play, Engagement, and Regulation (JASPER) focuses on social com-

munication skills; in Discrete Trial Training (DTT), therapists break target skills down into smaller steps. Another approach, called Strategies for Teaching based on Autism Research (STAR), applies PRT and DTT to classrooms.

A newer class of therapies targets social communication difficulties. Instead of using rewards to change behaviors, these therapies give a child practice engaging in social interactions. For example, in a therapy called Preschool Autism Communication Trial (PACT), therapists teach parents to recognize and respond to their child's attempts to communicate.

## How long does it take for early intervention to be effective?

Children receive ABA-based early intervention for up to 40 hours per week. The therapies may continue for several years, becoming shorter and less frequent at about age 5.

In light of this time commitment, parents are often tempted to try less established therapies billed as quick fixes or miracle cures, says Stephen Camarata, professor of hearing and speech sciences and psychiatry and behavioral sciences at Vanderbilt University in Nashville, Tennessee. Helping children learn skills can take a long time, however. "That's not a quick process, and it's not a magical process," he says.





## Is there evidence that these therapies are effective?

Surprisingly little. Most early interventions have not been tested in randomized controlled trials, says Tony Charman, chair of clinical psychology at King's College London. For instance, only one of the five studies included in a review last year was randomized; that study suggested that autistic children who receive therapy are more likely than untreated ones to be placed in mainstream classrooms.

Even when controlled trials exist—as they do for JASPER and ESDM—they often have too few participants to lead to firm conclusions about efficacy, Charman says. In a large analysis published earlier this year, trials that showed some positive effects had small sample sizes and effect sizes.

And, as in other areas of autism research, studies of early intervention have a diversity problem. Many studies predominantly include white children, so the results may not apply to other autistic children. Few studies compare therapies with each other, or track whether their effects last.

“We don't have very much evidence about what these interventions do after 20 years,” says Sally Rogers, professor of psychiatry and behavioral sciences at the University of California, Davis.

## When should treatment start?

Early intervention typically follows an autism diagnosis, so its start depends on the age of diagnosis. In the United States, most children are diagnosed after age 4.

It may be possible, and preferable, to start treatment even earlier in some cases. So-called ‘baby sibs,’ or children who have an older sibling with autism, are at an elevated risk for the condition. A study last year showed that two years after receiving five months of a video-based therapy to improve communication between parents and children, baby sibs showed some improvement in their skills.

A 2014 study of 11 infants showed that those who received an adaptation of ESDM between 7 and 15 months of age had fewer autism features at age 3 than those who did not receive therapy. The following year, a review of nine studies hinted that behavioral treatments improve social communication when applied in children under 2 years.

## How have behavioral treatments for autism changed over time?

Behavior therapies historically involved seating a child at a table for hours and asking her to name objects pictured on flash cards. Rigid drills like this can improve language, for instance, or ease repetitive behavior.

But over the past 20 years, therapies have moved to more familiar environments, such as the child’s bedroom or playroom. Often, a child gets to choose the activity—coloring at a table or playing with trucks, for example.



**EARLY  
INTERVENTION  
OFFERS THE  
BEST PROMISE  
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WELL-BEING.**

The intervention is often integrated into other aspects of the day, as parents have become increasingly important partners in reinforcing behaviors. Many researchers emphasize that the most effective interventions are those that can be adapted to an individual child. Children have specific developmental goals—related to language, say, or social skills—and start at various developmental levels.

“Interventions are not one-size-fits-all,” says Lynn Koegel, clinical professor of psychiatry and behavioral sciences at Stanford University in California, who is one of the creators of PRT.

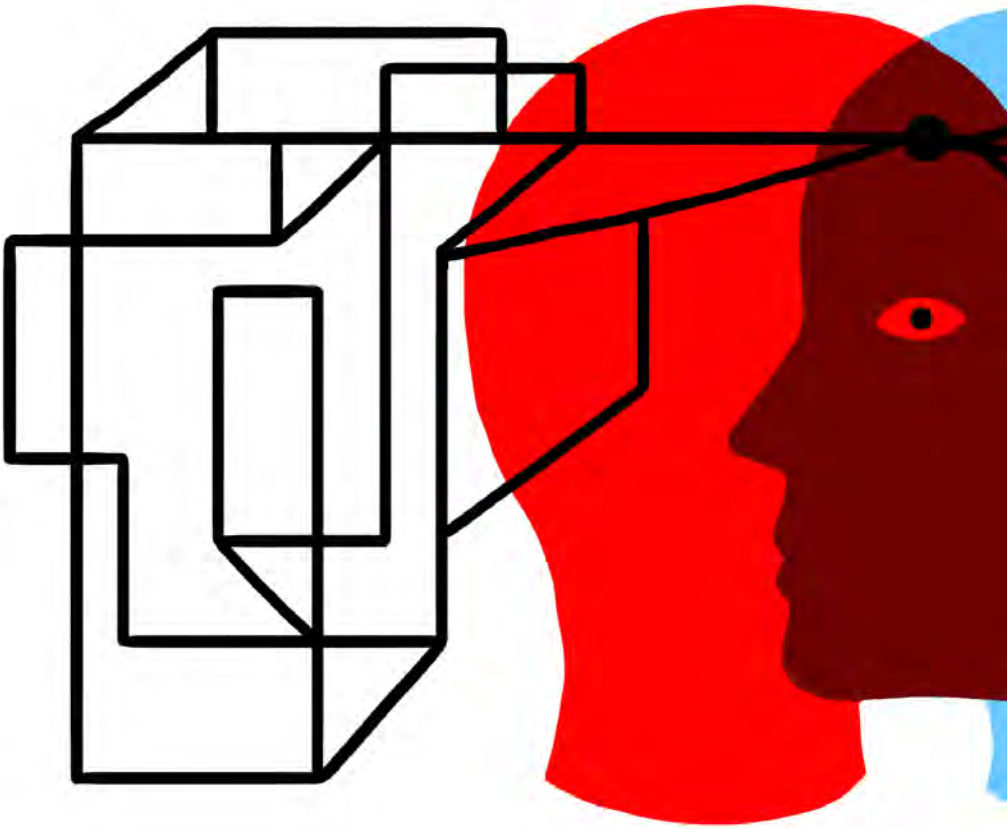
## What’s next for the field?

When an intervention proves effective, researchers often don’t know which components of it led to the improvement, making it difficult to incorporate it into new therapies. Some teams are trying to pinpoint the ‘active ingredients’ of successful treatments.

In 2015, a research team tested three components of the STAR method in 119 schoolchildren. One component, PRT, is associated with improvements in the students’ cognitive ability, the team found; the other components, DTT and a method called ‘teaching in functional routines’ are not.

A better understanding of the most important components of a therapy may provide clues to how to improve it. It would also help clinicians customize the therapy without inadvertently omitting the crucial ingredient.





25 JULY 2018

# Conditions that accompany autism

by Hannah Furfaro



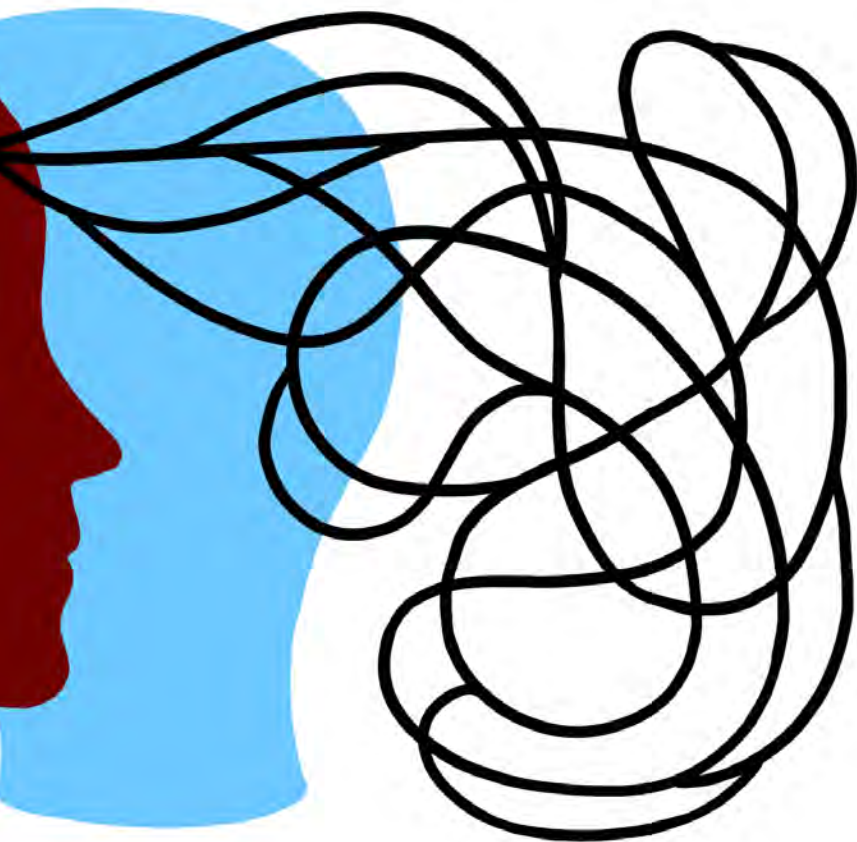


illustration by LAURÈNE BOGLIO

More than half of people on the spectrum have four or more other conditions.

The types of co-occurring conditions and how they manifest varies from one autistic person to the next. These conditions can exacerbate features of autism or affect the timing of an autism diagnosis, so understanding how they interact with autism is important. Here is what researchers know about the conditions that often accompany autism.



## Which traits or conditions commonly accompany autism?

The conditions that overlap with autism generally fall into one of four groups: classic medical problems, such as epilepsy, gastrointestinal issues or sleep disorders; developmental diagnoses, such as intellectual disability or language delay; mental-health conditions, such as attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder or depression; and genetic conditions, including fragile X syndrome and tuberous sclerosis complex.

## How common are these conditions among people with autism?

It depends on the condition, and estimates vary widely. For instance, between 11 and 84 percent of autistic children also have anxiety. Similarly, serious sleep problems may affect anywhere between 44 and 86 percent of children on the spectrum. Differences in diagnostic criteria and other study variables may explain these wide margins. And the age, sex, race and intelligence quotient of the person being evaluated can all influence whether and when they are diagnosed. For instance, autistic black children are more likely than autistic white children to be diagnosed with intellectual disability.

And if a child doesn't speak, mood disorders may be difficult to detect. Certain conditions, such as anxiety, may also look different in people with autism than they do in other people, adding another layer of complexity.

What's more, the tools used to identify the conditions may not work as well in people with autism. Researchers are developing autism-specific scales, such as a depression-screening questionnaire, to help solve these diagnostic puzzles.

## What can scientists gain from studying these conditions?

Nearly all conditions that accompany autism can have serious effects on well-being. And some have more severe consequences than autism does.

A better understanding of these conditions could improve quality of life for autistic people. For instance, identifying the genes involved could lead to early detection—and treatment—of the conditions.

“We really need to understand the roots of problems in mood and depression, as well as problems of impulsivity,” says Paul Lipkin, director of the Interactive Autism Network at the Kennedy Krieger Institute in Baltimore. “As we identify better understandings of the neurologic roots of these, we can hopefully develop more and better targeted medical treatments for them.”

Treating a related condition may also ease autism traits. For instance, treating seizures early may decrease cognitive and behavioral problems in children with tuberous sclerosis complex.



Resolving sleep or gastrointestinal problems may also offer behavioral benefits. Sleep quantity and quality can affect mood and the severity of repetitive behaviors, for example.



## How might co-occurring conditions complicate autism diagnosis?

Some autism traits, such as poor social skills and sensory sensitivities, overlap with those of other conditions. For instance, people with autism and those with schizophrenia both have trouble picking up on social cues. When a person presents with one of these common traits, her doctor may simply assign to her the most plausible diagnosis. “It can be very hard to figure out what the root of a behavior is,” says Carla Mazefsky, associate professor of psychiatry at the University of Pittsburgh.

ADHD traits may also mask or be mistaken for those of autism—and delay when a child receives an autism diagnosis.

Autism diagnosis may be particularly tricky in people with intellectual disability or severe language delays.

## What can studies of co-occurring conditions reveal about the biology of autism?

Some of these conditions may share biological mechanisms with autism. For instance, a study published this year revealed that gene-expression patterns in the brains of people with autism are similar to those in people with schizophrenia or bipolar disorder. People with these conditions may also share genetic variants and traits, such as language difficulties or aggression.

In other cases, the relationship to autism may be multifaceted. For instance, about one in three people with autism has epilepsy—and people with epilepsy are at an eightfold risk of autism compared with the general population. The connection may be partly genetic, but it is also possible that early seizures pave the way for certain autism features.





19 APRIL 2018

# Social communication in autism

by Lydia Denworth

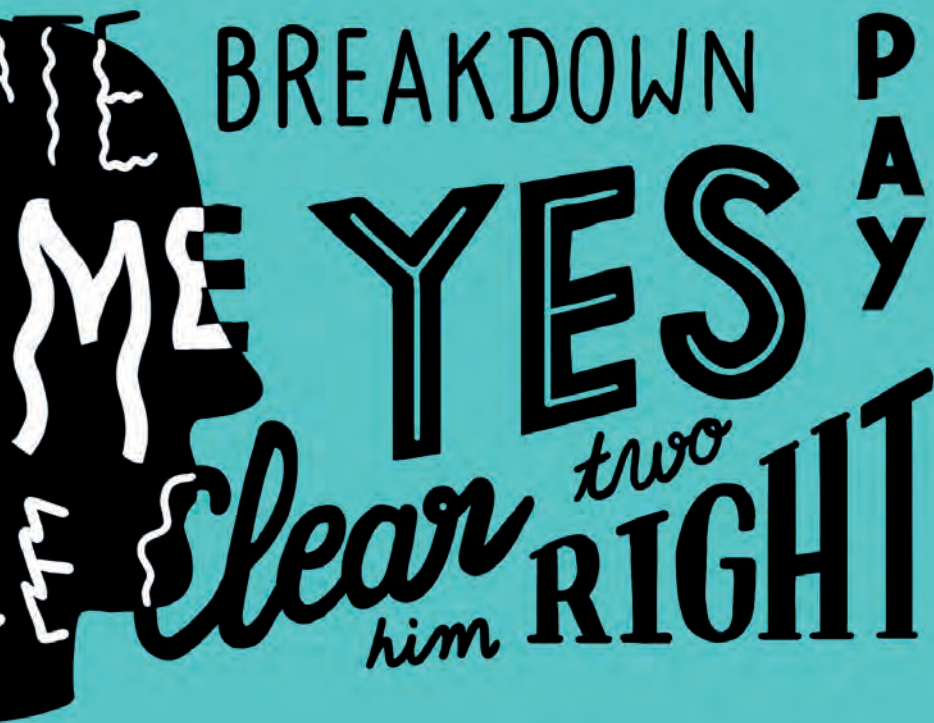


illustration by LAURÈNE BOGLIO

Communication problems have always been considered a core feature of autism. Yet there are substantial and wide-ranging differences in how people with autism communicate. That reflects not only the inherent variability of the condition, but also the complexity of communication itself—encompassing the words we use, the order in which we use them, eye contact, facial expressions, gestures and other nonverbal cues.

Challenges in any of these areas can contribute to the social difficulties individuals on the spectrum experience.

## What is social communication?

Social communication may seem like a redundant term. Communication is inherently social: It requires the ability to share—in an appropriate manner—what you feel or want to say, and also to understand and respond to what others are feeling or saying. In neurotypical people, communication disorders can include problems with language, but not with social interaction. People with autism, though, are particularly challenged by communicating in social contexts. Experts use the phrase ‘social communication’ to emphasize that fact.

## When were social communication difficulties first recognized as part of autism?

When Leo Kanner wrote his first paper on autism in 1943, his descriptions of the children he had observed included many problems with social communication. He noted, for example, failure to make eye contact or respond to questions, and a tendency toward obsessive conversation. Since then, language and communication impairments have consistently been part of the concept of autism, but not always a separate criterion for diagnosis.

As researchers have learned more about how language develops in people with autism, perspectives have shifted, more



than once, on how and whether to consider language and social interaction as separate or joint problems. For many decades, the focus was on individuals with severe autism, who may have few words, rarely initiate interactions and barely respond. Accordingly, an autism diagnosis called for a marked impairment in conversational abilities. But clinicians began to recognize that people with autism can have strong verbal skills. Initially, those people didn't appear to have any social communication problems either, but the past decade has shown that they are often regarded as 'awkward' in the way they communicate, and make more language errors than their typical peers. The latest thinking acknowledges that language is an integral part of social communication, and that social communication as a whole is a persistent problem for many people with autism.

## What sorts of problems with social communication are most common in people with autism?

Individuals on the spectrum have been shown to face challenges with a range of verbal and nonverbal skills, including grammar, the correct use of pronouns and responding when spoken to. Differences in some nonverbal aspects of communication, such as facial expressions and the tempo of speech, may account for what others perceive as 'awkwardness' in people with autism.

As with so many autism features, there is tremendous variability from one person to the next. Still, problems with two aspects of communication stand out: pragmatics and prosody.



## What are pragmatics and prosody?

Pragmatics is the appropriate use of language in social situations. Examples include being able to stay on topic and take turns in a conversation, ask appropriate questions and use a tone of voice suitable for the setting (for instance, a quieter voice in a classroom versus a playground). Many autism therapies incorporate explicit training on these skills.

Prosody is the rhythm of speech and encompasses aspects of both verbal and nonverbal communication. Carried in the spoken words and the pauses in between, prosody has multiple functions. For one, it conveys pragmatic information. A rising tone, for instance, indicates a question. Prosody also communicates emotion. The question ‘What do you mean?’ can be positive, negative or neutral depending on how it’s spoken; prosody is what alerts a listener to the difference.

Problems with prosody can vary. Some individuals speak in a monotone, whereas others exaggerate high and low pitches so dramatically that listeners find their speech unnatural.

## Can problems with social communication exist outside autism?

In 2013, the “Diagnostic and Statistical Manual of Mental Disorders” (DSM-5) added a new diagnosis: social communication disorder (SCD). This condition shares many of the traits common among people with autism, such as difficulty

responding to others, using gestures, staying on topic, and making and keeping friends. But individuals diagnosed with SCD do not show repetitive behaviors or restricted interests. Not all researchers agree, however, that SCD should be a separate diagnosis: They argue that there's not enough evidence that SCD is a valid and reliably distinct condition separate from autism.

## Where is research on social communication headed?

Clinicians are working to improve therapy for pragmatics because it is broadly relevant to most people on the spectrum. A few researchers are focusing on identifying subtler problems with social communication that make interactions challenging even for individuals with strong language and cognitive skills. New acoustic analysis and motion-capture technologies are allowing for detailed measurement of vocal pitch, among other variables, and of minute movements that make up facial expressions.

Communication between people with and without autism is a two-way problem. Individuals on the spectrum may have communication challenges to address, but their typical peers and conversation partners could do more to meet them halfway by accepting differences in the way they express themselves.





13 NOVEMBER 2017

# Sleep problems in autism

by Hannah Furfaro

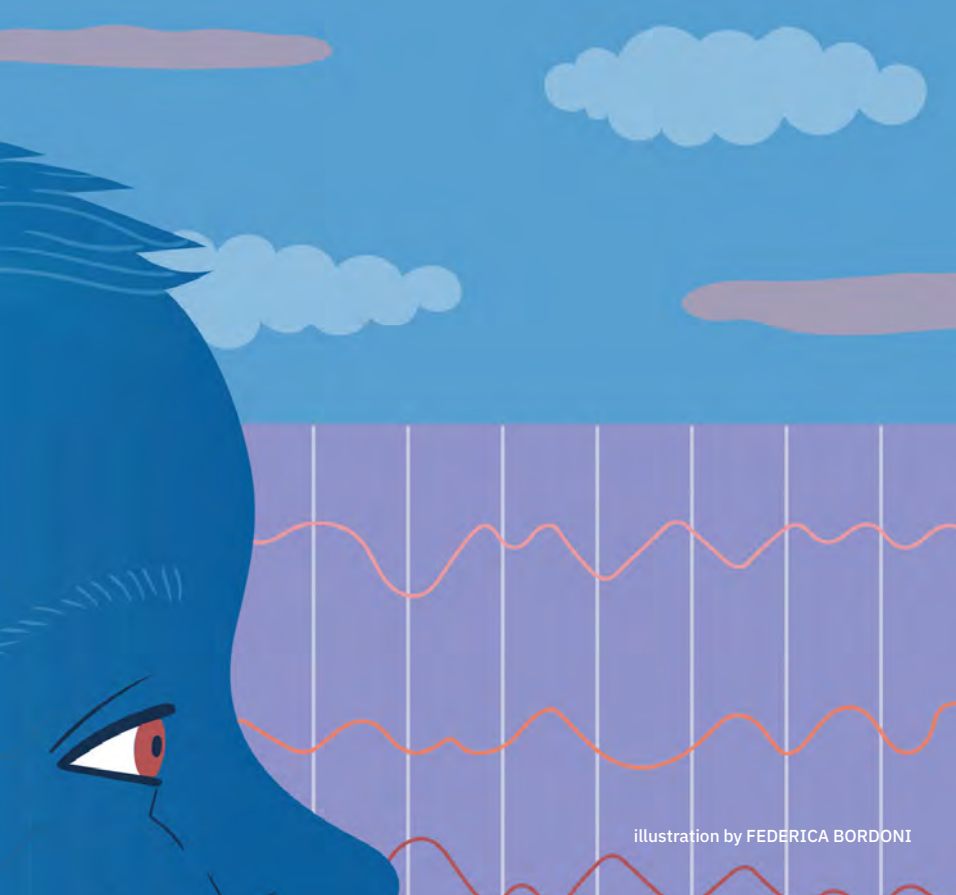


illustration by FEDERICA BORDONI

A good night's rest isn't guaranteed for anyone, but it is downright elusive for many people with autism. Individuals on the spectrum often have trouble falling and staying asleep.

And that may worsen certain features of their condition, such as repetitive behaviors, which can, in turn, make sleeping even more difficult.

Given this disruptive feedback loop, sleep problems are among the most urgent concerns for families grappling with autism. But so far, this also happens to be among the least-studied aspects of autism.

Here's what researchers know so far about the causes and consequences of—and treatments for—sleep problems in autism.



## How common are sleep problems in children with autism?

Between 44 and 86 percent of children with autism have a serious problem with sleep. By comparison, between 10 and 16 percent of children in the general population have difficulty sleeping. This range among people with autism may be wide because studies use different measures to study sleep.

## What types of sleep problems are common in autism?

People with autism tend to have insomnia: It takes them an average of 11 minutes longer than typical people to fall asleep, and many wake up frequently during the night. Some people with the condition have sleep apnea, a condition that causes them to stop breathing several times during the night.

Sleep in people with autism may also be less restorative than it is for people in the general population. They spend about 15 percent of their sleeping time in the rapid eye movement (REM) stage, which is critical for learning and retaining memories. Most neurotypical people, by contrast, spend about 23 percent of their nightly rest in REM.

## Does this lack of good sleep have consequences?

There is mounting evidence that too little sleep can exacerbate autism features, such as poor social skills. Children who do not get enough sleep often have more severe repetitive behaviors and a tougher time making friends than other people on the spectrum. They also tend to score lower on tests of intelligence. However, it is unclear whether these problems stem from poor sleep, contribute to it or both.

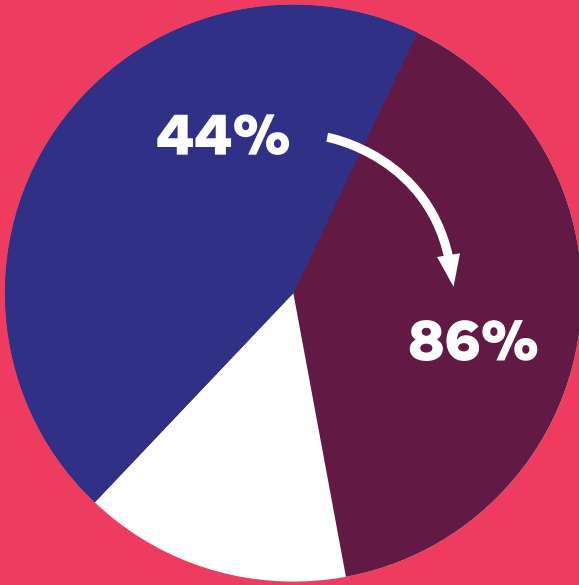
One 2009 study found that children with autism who have sleep difficulties are more hyperactive and easily distracted than those who sleep well.

## Why do people with autism have difficulty sleeping?

Many people with autism have other conditions, such as gastrointestinal problems, attention deficit hyperactivity disorder (ADHD) or anxiety, and each of those is known to disrupt sleep. Cramps from constipation, for instance, may keep a person with autism up at night.

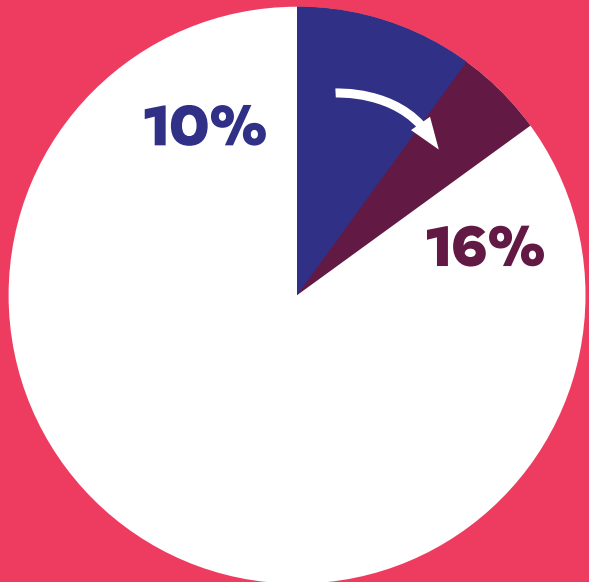
People with these other conditions may also take medications that affect sleep. For example, many people with ADHD take stimulants, which are known to cause insomnia.





**Children with autism who have difficulty sleeping**

**Children in the general population who have difficulty sleeping**





In some cases, people on the spectrum carry mutations that make them prone to sleep problems. A 2015 study suggests that individuals with autism are twice as likely as typical people to have mutations in genes that govern the sleep-wake cycle. Some studies suggest that people on the spectrum carry mutations that affect levels of melatonin, a natural hormone that controls sleep.

## How can researchers assess sleep problems in people with autism?

Polysomnography is the most common and thorough type of sleep test. It tracks a person's brain waves, eye and limb movement, and breathing patterns during sleep. Because it requires multiple sensors, wires and computers, it is typically done in a lab.

But this gold-standard method is not always practical for people with autism, many of whom require specific routines at bedtime. At least one research group has brought polysomnography equipment into the homes of people with autism to try to get around this problem.

A less cumbersome sleep test is actigraphy, in which a wristwatch-like device records a person's movements throughout the night. People can use the device at home to record the amount of time a person sleeps each night.

Researchers can also learn about sleep patterns by interviewing families or asking them to maintain sleep diaries. But these methods are error-prone because they rely on people's memories.





## Are there treatments available to help people with autism sleep better?

In some ways, the fix can be straightforward: Establishing a routine, such as an order of activities at bedtime, can often help a person fall asleep; so can changing the temperature or lighting in a bedroom. Sticking with regular bed and wake times can put the brain and body on a schedule that makes sleep more reliable.

The U.S. Food and Drug administration has approved insomnia drugs, such as Ambien, for adults with autism but not for children. For more serious problems such as sleep apnea, clinicians sometimes recommend a nighttime breathing device such as a continuous positive airway pressure (CPAP) machine or, in rare cases, surgery.

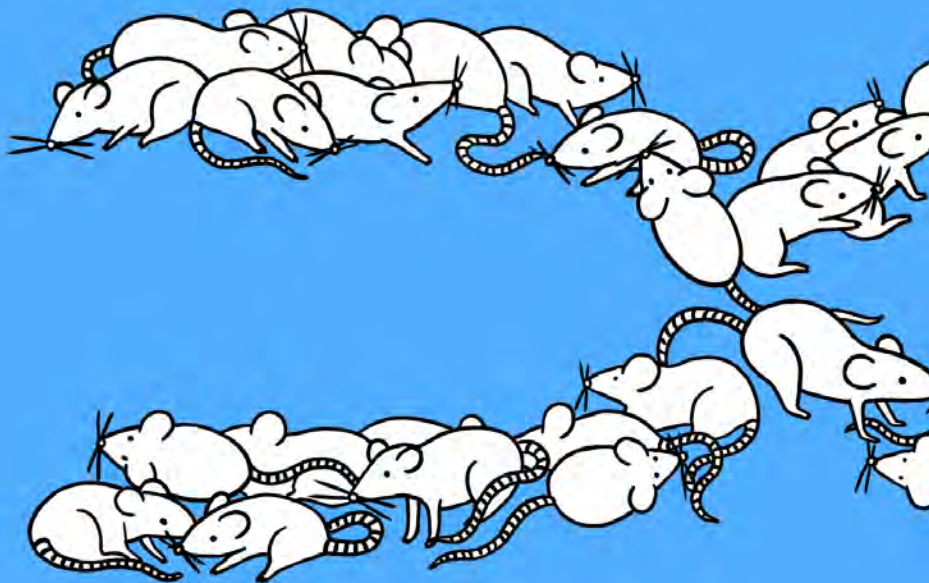
But for many sleep issues, melatonin supplements may be a good option. Some research suggests the supplements help children with autism fall asleep faster and get better-quality sleep.

# Would better sleep improve quality of life for people on the spectrum?

Maybe. No large, definitive study exists on this topic. But research has shown that typical children and those with autism who undergo surgery to alleviate breathing trouble during sleep show better social communication and attention as well as fewer repetitive behaviors. Parents reported similar improvements in a small study of children with autism who took melatonin supplements.

Better sleep is “not going to cure autism,” says pediatrician Angela Maxwell-Horn, assistant professor of pediatrics at Vanderbilt University in Nashville, Tennessee. But, she says, children with autism who get back on a regular sleeping schedule seem to learn better, are less irritable and have fewer problem behaviors.





10 OCTOBER 2018

# Fragile X syndrome's link to autism

by Hannah Furfaro

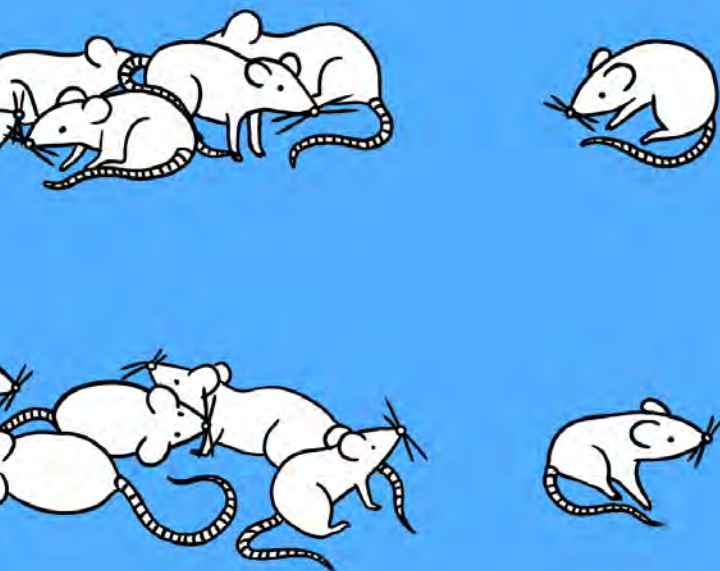


illustration by LAURÈNE BOGLIO

Fragile X syndrome is a leading genetic cause of autism. About one in three people with the syndrome also has autism. But even those who do not have autism often share certain autistic traits, such as avoidance of eye contact and difficulties in social situations. Mutations in the gene *FMR1*, which cause fragile X syndrome, account for up to 5 percent of autism cases.

For these reasons, research on fragile X can provide insights into the biology of autism and its treatment. Here is what scientists know about the mechanisms that underlie fragile X and some research angles they are pursuing.



## What is fragile X syndrome?

Fragile X syndrome is the most common cause of intellectual disability. It affects roughly 1 in 4,000 men and about half as many women. People with the syndrome also tend to have unusual physical features, such as a long face, large ears and flat feet. Some men have large testes, and some people with the condition have seizures.

## What is the relationship between fragile X syndrome and autism?

Almost 50 percent of men and 16 percent of women with fragile X also have autism, according to the U.S. Centers for Disease Control and Prevention. Other studies have hinted that up to 90 percent of men with fragile X have some autism traits, such as a tendency to avoid eye contact. Studies indicate that these traits may present differently in the two conditions. For instance, people with fragile X may show a few classic repetitive behaviors, such as hand-flapping, whereas autistic people typically have a broad range of repetitive behaviors, restricted interests or both. People with fragile X and those with autism may also have divergent developmental trajectories: For instance, social problems may worsen more, or more rapidly, in autistic people than in those with both autism and fragile X.

## What causes fragile X?

In most cases, the syndrome is caused by a mutation in FMR1, located on the X chromosome. People with fragile X have more than 200 repetitions of a sequence of three nucleotides, 'CGG,' at the start of the gene; typical people have 54 or fewer of these repeats. Under a microscope, this CGG expansion can cause the tip of the X chromosome to appear 'fragile.'

The expanded repeats can silence the production of a protein called FMRP. This protein serves critical functions, such as controlling the production of proteins at synapses, the junctions between neurons.

The leading theory of fragile X holds that when FMRP is missing, protein synthesis can run rampant and disrupt cognitive processes. A study published last month, however, has complicated scientists' understanding of the syndrome: It hints that loss of FMRP instead causes a dearth of proteins.





## What is the fragile X syndrome ‘premutation’?

The fragile X ‘premutation’ is defined as having 55 to 200 CGG repeats in FMR1. The premutation tamps down production of FMRP but does not silence it. Because premutation carriers may not show outward signs, the prevalence of premutations is unknown. Estimates range from 1 in 148 to 1 in 291 in women and from 1 in 290 men to 1 in 855 in men in the United States.

Some women with the premutation develop a condition called fragile X-associated primary ovarian insufficiency, which can trigger early menopause.

Both men and women with the premutation may develop a condition called fragile X-associated tremor/ataxia syndrome, which causes tremors and cognitive problems. The risk of developing this condition increases with age: Estimates suggest 30 percent of affected men and 8 to 16.5 percent of affected women over age 50 have it.

The repeats of the premutation can sometimes expand in future generations to the full syndrome. The more repeats in the mother’s premutation, the greater the chance the child will have a full mutation.

Some people have between 45 and 54 CGG repeats—a so-called ‘gray zone’ mutation. Little is known about the effects of this mutation, although evidence suggests it can lead to some features of fragile X-associated tremor/ataxia syndrome.



## Are there animal models available to study fragile X?

Researchers have developed mouse and rat models of fragile X syndrome by deleting FMR1. The brains of these mice respond abnormally to social stimuli, such as meeting a new mouse. The mutant mice also show alterations in a brain circuit involving the prefrontal cortex, which plays a role in social cognition.

Whether insights from the mice apply to people with the condition is unclear. The behaviors seen in mice that lack FMR1 are often inconsistent—and in many cases do not resemble those in people. For instance, the mutant mice do not show cognitive problems, one of the core features of fragile X. An animal model that faithfully mimics the syndrome would help researchers test treatments and trace the syndrome's origins.

## Are there treatments for fragile X syndrome?

A range of available behavioral therapies may improve speech and language abilities in people with fragile X. But there are no approved drugs for the syndrome.

Researchers are investigating many candidate drugs, including several that block a protein called mGluR5. Some of the candidates, such as arbaclofen and mavoglurant, have been shown to restore protein production and ease problems with learning and memory in the mutant mice. But none of the drugs has fared well in clinical trials.



**ALMOST  
50% OF MEN  
AND 16% OF  
WOMEN WITH  
FRAGILE X  
ALSO HAVE  
AUTISM.**

That may be because the trials used the wrong markers to measure the drugs' effectiveness. Or it may be because the trials involved adolescents and adults, whose brains may no longer respond to intervention. One team is testing mavoglurant in young children and using a test of language learning to measure its effectiveness. They plan to pair the drug with an intensive language intervention.

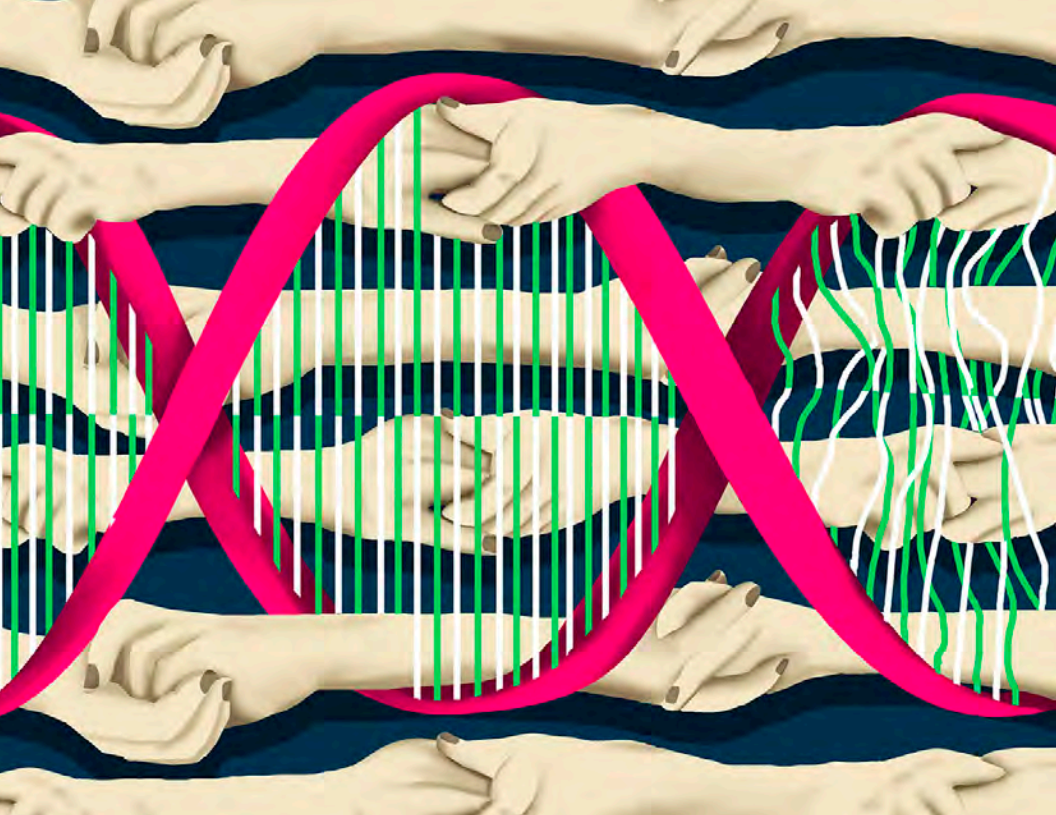
Other teams are testing a drug called lovastatin, which is used to treat high cholesterol levels and has been shown to reduce seizures in fragile X mice.

Researchers are also testing a drug that targets the enzyme PDE4D and seems to improve social behaviors in the mutant mice.

## What are the next steps for the field?

Researchers are pushing to develop good outcome measures for clinical trials and to investigate promising drug candidates. Other efforts aim to clarify the functions of FMRP or to repair the mutation. In a March study, for example, researchers used a gene-editing tool to remove chemical tags from CGG repeats in cells from a person with fragile X. The treatment restored FMRP expression to 90 percent of normal levels.





21 OCTOBER 2019

# Rett syndrome's link to autism

by Sarah DeWeerd

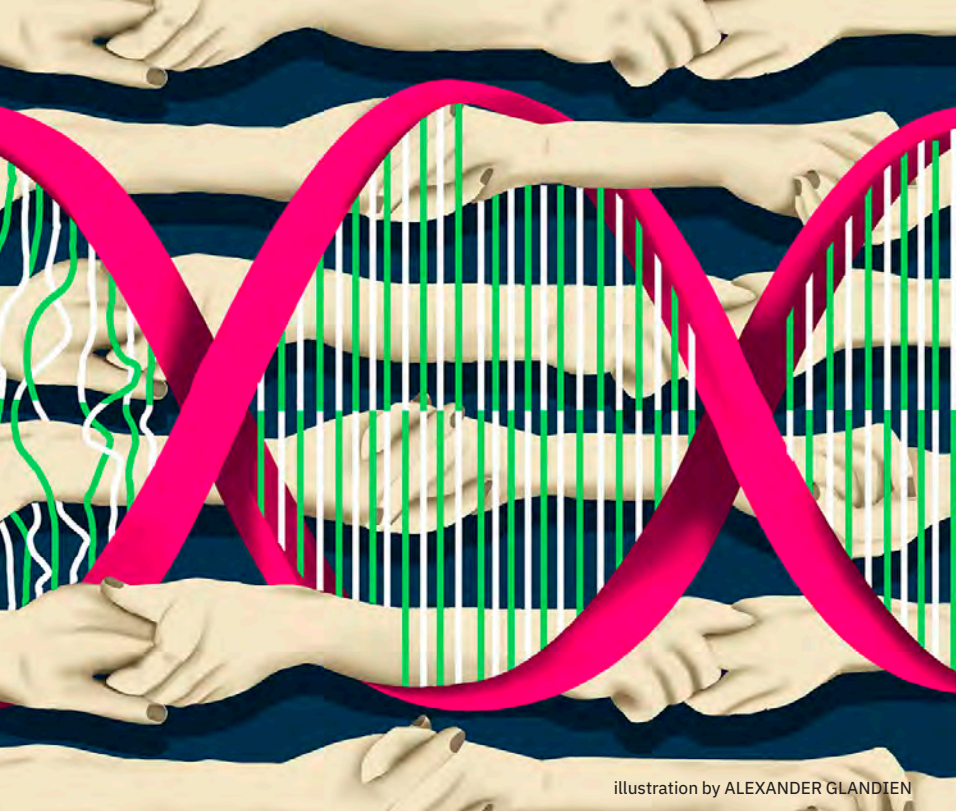


illustration by ALEXANDER GLANDIEN

Austrian pediatrician Andreas Rett first recognized the syndrome that would later bear his name in the mid-1960s. The first description in English, published in 1983, detailed a “progressive syndrome of autism” and other traits in 35 girls.

Rett syndrome usually arises from mutations in the *MECP2* gene on the X chromosome. Children who have it—virtually all of them girls—become withdrawn, develop repetitive hand movements and often lose the ability to speak and walk. The mutations are usually fatal in boys soon after birth, but a few survivors have mild mutations or atypical forms of the syndrome.

Mouse models of Rett syndrome are yielding insights into the brain cells and circuits that may be involved in the syndrome, and also in autism. Studies of Rett may even point to autism treatments.





## What do Rett syndrome and autism have in common?

Quite a lot. Like autism, Rett syndrome is not apparent at birth; in both conditions, a period of apparently typical development precedes the onset of early signs.

Those signs, as well as their timing, are similar for both conditions. Between the ages of 6 and 18 months, children with Rett syndrome withdraw from social interaction and lose the ability to speak. At the same age in autistic children, parents and caregivers may notice a lack of social interest as well as communication problems.

Regression, the loss of previously acquired skills, is a hallmark of Rett syndrome. At least one in five children with autism also experiences regression. The regression happens at about the same time in both conditions and involves similar trends: loss of language and social skills.

Repetitive behaviors are common in both conditions, too. In Rett syndrome, repetitive hand movements—usually hand-wringing or touching the hands to the mouth—are often so frequent they prevent the children from using their hands in a purposeful way. The repetitive behaviors associated with autism are more varied and may include spinning, body-rocking and grinding of teeth.

Autistic people also often show cognitive forms of these behaviors: routines, rituals or an intense focus on a specific interest.

Other features, such as anxiety and seizures, are also common in both conditions.


## Are there differences between the two conditions?

Yes, and some are significant. For example, atypical social behavior is a defining characteristic of autism. But in people with Rett syndrome, the loss of social interest is often temporary: Over time, many girls with Rett syndrome become socially engaged again. And whereas many people with autism avoid eye contact, those with Rett syndrome often learn to use eye movements to communicate their wishes.

Movement problems in people with Rett syndrome tend to be much more severe than those in autistic people. People with autism may have poor coordination or an awkward gait. But many girls with Rett syndrome are unable to walk, and as they get older they may develop rigidity or tremors.

Rett syndrome also involves problems with the autonomic nervous system that may lead to fatal breathing abnormalities, a problem not seen in autistic people.





# What can studies of Rett syndrome tell us about autism?

Scientists are investigating how regression unfolds in Rett syndrome in hopes of better understanding regression in autism. One hitch is that Rett mouse models do not show the loss of motor coordination and communication skills seen in people with the syndrome.

Some researchers are manipulating MECP2 in specific cells or regions of the mouse brain to pinpoint the source of Rett syndrome traits. Deleting the gene only in inhibitory neurons, which dampen brain signaling, can produce most of the syndrome's traits, including social deficits and motor problems. So, the signaling molecule gamma-aminobutyric acid, which is released from inhibitory neurons, is likely to be important in Rett syndrome, as it is in autism.

Mice lacking MECP2 in specific types of inhibitory neurons or in excitatory neurons have other combinations of Rett traits. Deleting genes from specific cell types or brain regions could also help researchers determine how autism features arise in the brain.



## What else do researchers know about the Rett syndrome gene?

MECP2 regulates the expression of thousands of other genes. Studying its function could help scientists understand other autism genes, such as CHD8, that are ‘master regulators’ of gene expression. MECP2 also regulates the expression of a large number of unusually long genes, some of which are known to be involved in autism.

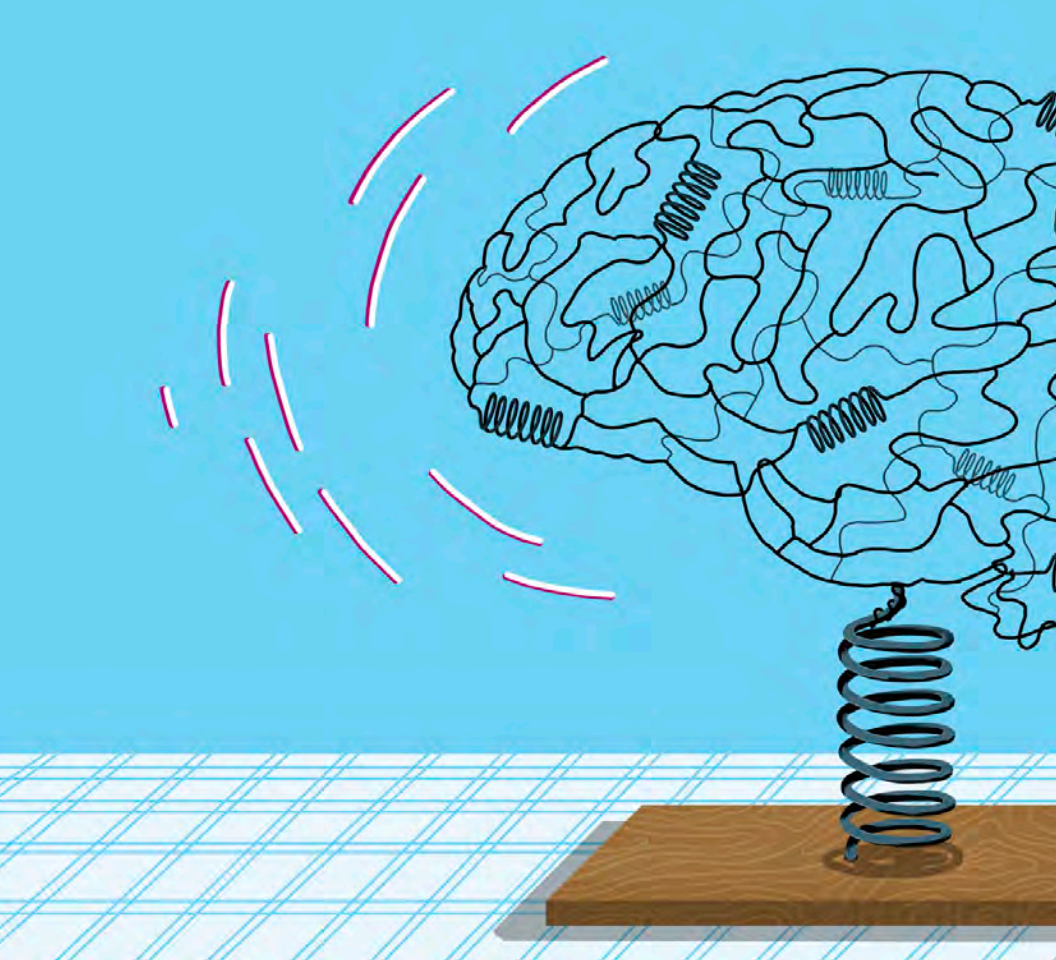
At least a dozen other genes that MECP2 controls have also been implicated in autism. These genes include FOXP1, GABRA3 and TBR1, and they may provide clues to molecular pathways involved in autism.

## Could studies of Rett syndrome lead to autism treatments?

Scientists aim to treat Rett syndrome using drugs to counteract the effects of MECP2’s absence on neurons, or with gene-therapy approaches that normalize brain levels of the protein.

Manipulating MECP2 is unlikely to help people with other forms of autism. But identifying brain circuits common to both conditions could point to treatments, such as deep brain stimulation, that target the circuits.





21 OCTOBER 2019

# The link between epilepsy and autism

by Jessica Wright

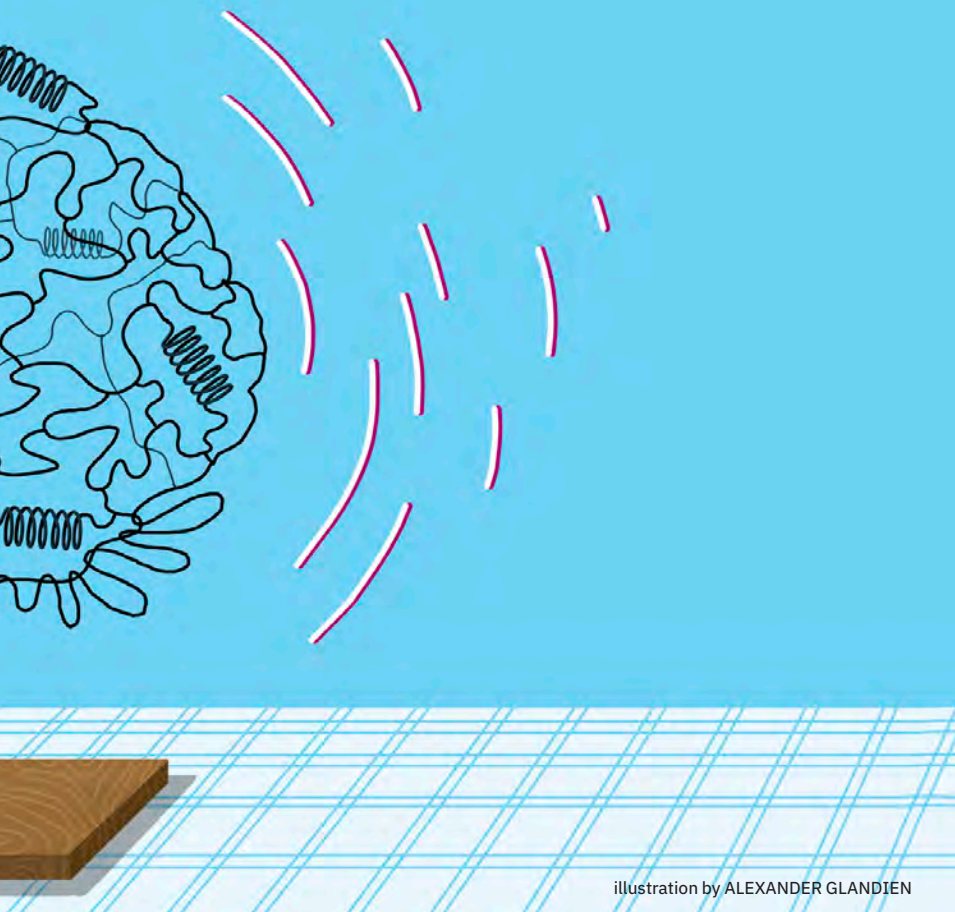



illustration by ALEXANDER GLANDIEN

Autism frequently co-occurs with any of a long list of other conditions. But none may be more closely linked than epilepsy. Nearly half of all autistic people have epilepsy, according to some reports, suggesting that the two conditions share underlying biology. For example, both conditions are characterized by overly excitable brains.

It's not yet clear whether epilepsy contributes to autism or is a consequence of the condition, however.





## What is the evidence that autism and epilepsy often co-occur?

One large study published in 2013 looked at nearly 6,000 autistic children and found that 12.5 percent have epilepsy. The proportion rose to 26 percent among children older than 13 years. A 2019 study of nearly 7,000 autistic children also found that about 10 percent have epilepsy. The number from other studies is highly variable, ranging from 2 percent up to 46 percent.

However, these estimates all exceed epilepsy's prevalence in the general population: 1.2 percent in the United States.

People with epilepsy are also more likely than others to have autism: A Swedish study of more than 85,000 people with epilepsy found that autism is 10 times more common in those individuals than in the general population.

## Is autism associated with a certain type of epilepsy?

Apparently not. Autistic people have been known to have most types of seizures, including generalized seizures, those that originate in a specific part of the brain, and severe spasms in infancy. Some studies have suggested that certain seizure types tend to be common among autistic individuals, but the findings may be skewed because the researchers recruited participants with only some forms of autism.

Epilepsy onset appears to occur at two peaks in autistic children: early childhood and adolescence. But as many as 20 percent of autistic people with epilepsy have their first seizure in adulthood.

## Are certain forms of autism more closely associated with epilepsy than others?

Perhaps. Several studies suggest that children who have both autism and intellectual disability are more likely to have epilepsy than other autistic children.

Autistic women are more likely to have epilepsy than are autistic men, according to some studies; roughly three boys are diagnosed with autism for every girl, but the ratio is less than 2-to-1 among those who have both epilepsy and autism. Motor problems, language difficulties and regression are all associated with epilepsy in an autistic person.



## Do autism and epilepsy share genetic risk factors?

Yes. Multiple lines of evidence suggest that autism and epilepsy stem from a common genetic origin. A 2013 study found significant overlap between genes linked to epilepsy and those tied to autism. And a 2016 study found that children who have an autistic older sibling are 70 percent more likely to have epilepsy than controls, even if they do not themselves have autism.

Researchers have linked mutations in several genes, including SCN2A and HNRNPU to epilepsy, autism or both. Certain genetic conditions related to autism, such as tuberous sclerosis or Phelan-McDermid syndrome, are also associated with epilepsy.

## What might explain this overlap between autism and epilepsy?

One theory for the overlap is that the conditions share common biological mechanisms. Epilepsy is characterized by too much excitation in the brain, which may stem from too little inhibition.

A landmark study published in 2003 proposed that autism may also stem from an imbalance between excitation and inhibition in the brain. There are data to support this theory from studies in both animals and people, but many experts remain skeptical.

## Can epilepsy contribute to autism traits?

There is some evidence to support this theory. Having severe epileptic seizures in infancy—in particular, a harmful type called infantile spasms—has been shown to have lasting consequences for the brain. And surgery to treat severe forms of epilepsy seems to lead to long-term improvements in social behavior and cognition.

To explore the link between seizures and autism, researchers are tracking the health of newborns who have tuberous sclerosis, a genetic condition that leads to both epileptic seizures and autism. The team has so far found that the children who have seizures in the first year of life are most likely to have developmental delay. The researchers aim to test these children for autism once they turn 3.

The same team has also designed a clinical trial to see whether preventing seizures during infancy in children with tuberous sclerosis improves their overall development and prevents a later diagnosis of autism.



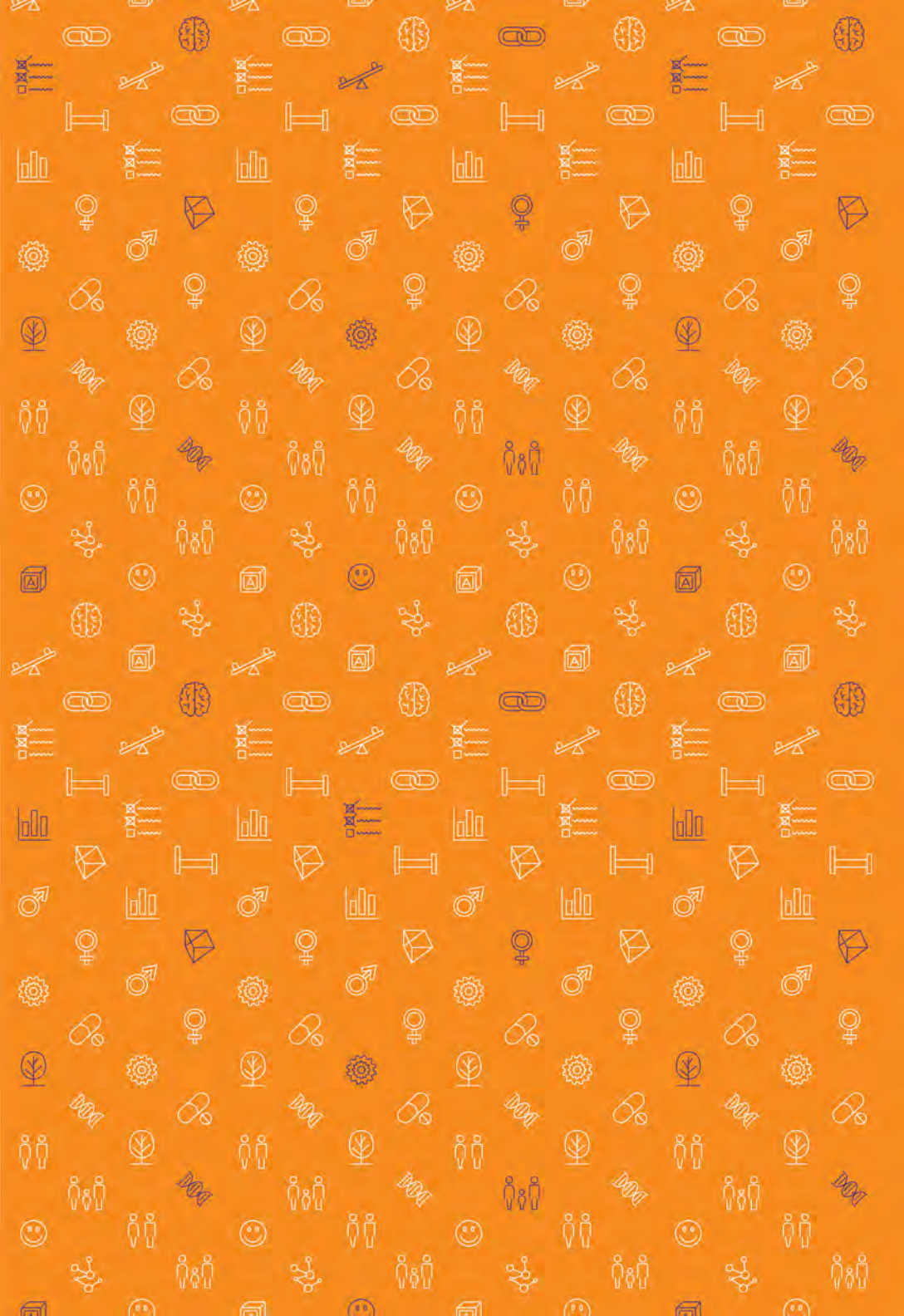
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