

DEEP DIVE

# Decoding the overlap between autism and ADHD

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Every morning, Avigael Wodinsky sets a timer to keep her 12-year-old son, Naftali, on track while he gets dressed for school. “Otherwise,” she says, “he’ll find 57 other things to do on the way to the bathroom.”

Wodinsky says she knew something was different about Naftali from the time he was born, long before his autism diagnosis at 15 months. He lagged behind his twin sister in hitting developmental milestones, and he seemed distant. “When he was an infant and he was feeding, he wouldn’t cry if you took the bottle away from him,” she says. He often sat facing the corner, turning the pages of a picture book over and over again. Although he has above-average intelligence, he did not speak much until he was 4, and even then his speech was often ‘scripted.’ He would repeat phrases and sentences he had heard on television.

Naftali’s trouble with maintaining focus became apparent in preschool — and problematic in kindergarten. He would stare out the window or wander around the classroom. “He was doing everything except what he was supposed to be doing,” Wodinsky recalls. At first, his psychiatrist credited these behaviors to his autism and recommended he drink coffee for its mild stimulant effect. The psychiatrist also suggested anxiety drugs. Neither treatment helped. A doctor then prescribed a series of drugs used for attention deficit hyperactivity disorder (ADHD), even though Naftali’s hyperactivity was still considered a part of his autism; those medications also failed or caused intolerable side effects.

Finally, when Naftali was 7, another doctor had Naftali’s mother and teachers fill out assessments of his behavior and concluded that Naftali has ADHD as well as autism.

Until about five years ago, the American Psychiatric Association’s diagnostic bible held the two conditions to be mutually exclusive: Only in 2013, with the debut of the current “Diagnostic and

Statistical Manual of Mental Disorders” (DSM-5), did **a dual diagnosis** become permissible. But in fact, autism and ADHD often coincide. An estimated 30 to 80 percent of children with autism **also meet the criteria for ADHD** and, conversely, 20 to 50 percent of children with ADHD for autism. Given the size of the overlap, scientists are beginning to rethink the relationship between the two conditions and to look for **common biological roots**.

The connections could run deep. One team in the Netherlands has proposed that autism and ADHD are different manifestations of a **single condition** with a range of subtypes, each having a distinct time of onset, mix of traits and progression. In this view, ADHD can occur without signs of autism, but autism always occurs with features of ADHD or other conditions, notes the team’s leader **Jan Buitelaar**, professor of child and adolescent psychiatry at Radboud University in Nijmegen, the Netherlands.

However tempting the ‘one-condition’ idea may seem, the evidence is far from conclusive. A growing number of genetic studies support the notion of at least **some shared causation** between autism and ADHD. But imaging studies comparing brain structures and connectivity have yielded a confusing mix of similarities and differences. And some behavioral research has highlighted the possibility that outwardly similar features mask distinct underlying mechanisms. Inattention in a person with autism, for example, might result from sensory overload, and apparent social problems in someone with ADHD may reflect impulsivity.

“Are we looking at one condition that’s on a continuum, or two distinct conditions? I think we don’t know the answer to that question,” says **Geraldine Dawson**, director of the Duke Center for Autism and Brain Development. “There hasn’t really been enough systematic research.”

Understanding how the two conditions intersect may, in any case, lead to improved therapies — a pressing need. People who have traits that stretch across both autism and ADHD diagnoses often face more serious challenges than people with either diagnosis alone: They can have **greater impairments** in adaptive functioning, a term that refers to self-care and daily living skills, and more severe **social and cognitive** issues.

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## Common ground:

The idea that autism and ADHD are intrinsically entwined stems not just from their frequent co-occurrence, but from observations that they share behavioral features. The core diagnostic criteria for the conditions remain distinct in the DSM-5: social communication impairments plus restricted

and **repetitive behaviors** for autism; and inattention or hyperactivity and impulsivity, or a combination, for ADHD. But both conditions can involve delays in language, heightened sensory responses, defiant behavior, problems with regulating emotions and difficulty with planning and with inhibiting behavior. Both also appear in childhood and are **more often diagnosed in boys**.

Some of the strongest support for shared roots comes from studies of families and twins, which indicate that relatives of people with either condition have an increased risk of having both. For instance, firstborn children of women with ADHD face a **sixfold risk of also having ADHD** and more than double the risk of having autism compared with the general population, according to a 2014 study.

Last year, another team considered the risks in reverse. Reviewing medical data from nearly 2 million people born in Sweden, they found that individuals with autism and their extended family members **have an elevated risk** of ADHD. As would be expected for highly heritable conditions, ADHD risk is highest among identical twins of people with autism, and is elevated even in cousins. The heightened vulnerability in cousins strengthens the idea of a genetic connection between the two conditions — because cousins are typically more genetically alike than nonrelatives but less likely than twins to have had the same environmental exposures early in development.

These results indicate that at least some shared genetic risk factors underpin both conditions. But the picture becomes murkier at the level of individual genes.

Autism and ADHD are both thought to involve multiple genes, many of which may individually exert small effects. Also, both conditions are heterogeneous, meaning the specific genes involved can differ from person to person. Adding to the complexity, the nature of the genetic influences can also vary. Some risk factors are so-called common variants — versions of genes that appear in more than 1 percent of the population. Unpublished research posted on the preprint server bioRxiv in November is among the first to find evidence of an **overlap in common variants** between people with autism and those with ADHD. Other risk variants are rare and tend to occur spontaneously, or may be inherited. Common and rare variants can both involve anything from single DNA letters to larger chromosomal segments encompassing multiple genes.

“Genetic studies of both common and rare variants are beginning to show that risk for ADHD and [autism] is at least partly shared,” says **Joanna Martin**, a researcher at Cardiff University in Wales, who studies the genetic risk of neurodevelopmental conditions. Still, scientists have yet to make a strong case implicating any particular **genetic variant in both autism and ADHD**. “Studies so far have been underpowered to conclusively identify specific risk variants that are shared,” Martin says.

One of the latest discoveries is that a certain kind of mutation, called a truncating mutation, is more

**common in people who have autism, ADHD** or both than it is in controls. In these rare mutations, a change in a single DNA base leads to an incomplete, and potentially malfunctioning, protein. A 2017 study examined sequences from the coding genomes of about 8,000 infants with autism, ADHD or both and more than 5,000 typical infants. A statistical analysis implied that many of the mutations occur in the same genes in both autism and ADHD, although it did not specify which ones.

## Puzzling ambiguity:

For all the buzz around the ‘shared-origins’ idea, the quest to find common roots could fall short. Evidence drawn from genetics, brain imaging and behavioral research all give reason to question whether autism and ADHD are related below the surface.

One genetic study last year focused on people with ‘sporadic’ ADHD, who have no relatives with the condition. The team first sequenced the coding genomes of 11 children and their parents, and found six noninherited mutations in 4 of the children. They then looked at whether the same 11 children, plus 117 others with sporadic ADHD, carry mutations in the coding regions of 26 genes **previously tied to autism** or intellectual disability. A mutation in only one of these genes appeared in a child with ADHD. The result “does not rule out some overlap but suggests that the origins may largely differ,” says lead investigator **Gail Jarvik**, head of the medical genetics division at the University of Washington in Seattle.

The case for shared causation is also difficult to nail down on anatomical grounds. Imaging studies paint a hazy picture of whether shared brain features contribute to autism and ADHD.

In 2016, researchers reviewed 23 years of structural **brain-imaging studies** in people with autism, ADHD or both. The studies examined the volume of different brain regions and assessed the integrity of the wiring in various areas. “Based on our review, we found both shared and different brain alterations in [autism] and ADHD,” says **Andrew Michael** of the Autism and Developmental Medicine Institute at Geisinger, based in Pennsylvania.

For instance, the team noted that, in general, people with one or both conditions have less robust wiring in the **corpus callosum**, which joins the brain’s two hemispheres, and in the **cerebellum**, which is involved in motor control and cognition. Both structures also tend to be smaller than usual in individuals with these conditions. At the same time, people with autism, but not those with ADHD, tend to have a large amygdala, which plays a role in **anxiety**, fear and social behaviors. And the total brain volume is also likely to be bigger in people with autism and smaller in those with ADHD, compared with controls.

Buitelaar and his colleagues have also reviewed brain imaging studies of people with autism or ADHD. They, too, saw a mix of findings, which they acknowledge are difficult to interpret. In keeping with their 'one-condition' hypothesis, though, they concluded that **brain maturation** in both conditions proceeds differently or is delayed compared with typical individuals. They hypothesize that distinct patterns of thinning in certain brain regions might help them to distinguish subtypes of their proposed autism-ADHD spectrum.

Imaging data aside, yet another fault line runs through the shared-origins idea: Behaviors that look similar in people with autism or ADHD may be unrelated, according to a 2016 review of the **early traits of children with autism** or ADHD. For instance, clinicians and parents may rate young children with either condition as having 'negative affect.' But this surface state often seems to stem largely from distress, shyness, fear or sadness in children with autism, and from anger in those with ADHD. Likewise, the DSM-5 inattention criterion for ADHD — not seeming to "listen when spoken to directly" — is often also seen in children with autism; in them, however, it may derive mainly from a difficulty in processing and attending to social cues.

In trying to determine whether autism and ADHD have common roots, researchers need to look at the motivations that impel a child's actions and reactions, says **Janne Visser**, a child psychiatrist in the Netherlands who worked on the study. Studying children from infancy into adolescence, she says, will help to clarify how the features of the conditions unfold and affect the children's development over time: One condition may lead to the other, or both may originate from a common set of risk factors, or the pathways may even converge over the course of development. "When you look at the first years of life," she says, "you can expect to get nearer to the origins."

Another approach researchers are using to explore the relationship between autism and ADHD is **focusing on traits**, or 'dimensions,' rather than attempting to connect genetic or brain features with diagnoses. Looking at overarching diagnoses, some experts say, produces too much noise, given that people with the same diagnosis can differ greatly in the mix and severity of the characteristics they display. "In reality, behavior is very dimensional," says Dawson, "and symptoms can go from very mild to severe, and you can have few symptoms or many."

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### **Clinical challenges:**

How best to treat children who, like Naftali, have a dual diagnosis is still unclear. The effectiveness

of ADHD medications can vary even in children who do not have autism. And children with autism **sometimes respond less well** than others or have more difficulty tolerating the drugs. “It is only through trial and error that we can make a judgment about how any particular child with ADHD will respond to any medication — including stimulants — whether or not they also have [autism],” says psychologist **Deborah Pearson** of the McGovern Medical School at UTHealth in Houston.

“I wish we knew more about what the most effective interventions are and how long we should be implementing them,” Pearson says. “What kinds of combined treatments would give us the very best outcomes?”

Dawson is co-leading three studies to improve treatment — and early detection. She and her colleagues plan to follow about 9,000 toddlers from 18 months to 3 years, screening them for both autism and ADHD at age 3. That study aims to find early signposts of ADHD in children with autism, in part to avoid **delayed diagnosis** of autism in children who also have ADHD. The researchers also intend to compare patterns of brain activity, attention and behavior in children with autism alone, ADHD alone or both. And they aim to examine whether stimulant drugs improve responses to early behavioral therapy in children with autism and ADHD.

In Naftali’s case, one of his doctors finally hit on an ADHD drug combination that helped — at least until early afternoon. “He’s going to be inattentive in the afternoon,” Wodinsky says. “We’ve all just kind of learned to live with that fact.”

Still, Dawson says she is optimistic that outcomes for children like Naftali can be improved. “We know the brain is very plastic,” she says. “So, if we can find kids early, I am always very hopeful that, regardless of the pathways involved, we can have a positive impact on early brain development.”

It’s a goal that resonates with Naftali’s parents.

They have been vigilant throughout his life about making sure he gets the services and care he needs. Wodinsky credits his having a best friend to the **hormone oxytocin**, which he started taking as part of a clinical trial and now takes twice daily. With help from his teachers, his ADHD medication and a structured schedule at home, Naftali is doing well in a class for typical children. He is still socially immature, but like many boys his age, he spars with his sister and enjoys Minecraft and other online video games.

“We never, ever say anything to him other than ‘You *will* go to college, you *will* get a job, you *will* get married.’ That’s what we plan for him,” his mother says. “There is no plan B.”

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