DEEP DIVE

Rethinking regression in autism

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Illustration by Kouzou Sakai

One of the oldest ideas in autism — as old as the naming of the condition itself — is that it comes in two forms: one present from birth, and one that abruptly emerges in toddlerhood. The latter type, or so the idea goes, announces itself through a rapid loss of skills.

In this classic picture of ‘regression,’ a talkative, curious 2-year-old suddenly withdraws. He grows indifferent to the sound of his name. He begins to speak less than before or stops entirely. He turns from playing with people to playing with things, from exploring many objects and activities to obsessing over a few. He loses many of the skills he had mastered and starts to rock, spin, walk on his toes or flap his hands. It’s often at this point that his terrified parents seek answers from experts.

This dichotomous view of the onset of autism is what **Sally Ozonoff** long held to be true. The textbooks and papers she read as a student in the 1980s described regression as a subtype of autism — an exception to the more common ‘early-onset’ version of the condition, which many considered innate. Studying autism, Ozonoff recalls, meant accepting this divide.

But in the decades since, these once-clear boundaries have started to fade. Epidemiological studies have found that anywhere from 15 to 40 percent of autism diagnoses fit the regressive type, with estimates varying wildly depending on how regression is defined. And regardless of the definition, **estimates of regression’s prevalence** (mainly as measured in the United States) have tended to rise as studies have become larger and more rigorous, Ozonoff says. This variability and expansion have both challenged the prevailing view of regression as an exception.

Today, Ozonoff, professor of psychiatry and behavioral sciences at the University of California, Davis MIND Institute, is one of a growing cohort of researchers who say the simple split between regressive and non-regressive autism is almost certainly wrong. Their proposal, which has gained momentum over the past 15 years, is that researchers and clinicians should retire the division for good.

"I think most kids with autism lose some skills, but how many they lose — and when they lose and what they lose — varies across kids," says **Catherine Lord**, director of the Center for Autism and the Developing Brain at New York-Presbyterian Hospital in New York City. "I think classifying them as regressive or non-regressive is a waste of time and a misnomer."

This idea was a major theme — the elephant that kept walking through the room — at a **conference on regression** that the U.S. National Institutes of Health held last February. One researcher after another described onset patterns of autism that defied the two-category view. Several, for example, reported that the more they scrutinized home videos or other contemporaneous records, such as clinician or caretaker reports from the first year of life in children ultimately diagnosed with regressive autism, the more they saw early signs of the condition.

The strength of these early signs varies, and they're often subtle, but they show up in multiple domains, from movement and eye-gaze patterns to language responses and social interactions. Regression should be seen not as an event but as a process — occasionally sudden but usually protracted, **Katarzyna Chawarska**, a researcher at the Yale Child Study Center, said at the meeting. Trying to separate the children who regress from those who don't, she said, "can be like drawing a line in the sand" — an unreliable marker in shifting terrain.

Chawarska's view echoes the findings of numerous studies that reveal a "**range of onset patterns**," as University of Melbourne autism researcher **Amanda Brignell** and her colleagues explain in a 2016 paper, from 'early onset' (early developmental delays, no loss of skills) and 'delay and regression' (some early delays, then loss) to 'plateau' (no early delays and no loss, but a failure to gain) and ordinary 'regression' (no delays before a clear loss). These trajectories differ so much in their timing, speed, depth and effects that it requires a tangle of words and parentheticals to try to squeeze them into a binary framework.

Given all this, Ozonoff argues, we should speak not of regression, but of a variety of onsets: The true clinical picture of how autism begins to present is not two-tone or even spectral, but a complex kaleidoscope of possibilities. "I don't even call it regression anymore," she says. "I just think of it as onset: how symptoms start."

The great divide:

To understand this shift from the innate-versus-regressive dichotomy, it helps to understand how that split took hold to begin with. It originated, as journalist Steve Silberman's **bestselling book "NeuroTribes"** describes, in Leo Kanner's **seminal 1943 paper describing autism**. In that study of 11 children, Kanner claimed to have identified a new developmental syndrome. Although this syndrome, autism, overlapped heavily with a broadly defined developmental condition others were then calling 'childhood schizophrenia,' Kanner argued it was unique in that it was present "from the very beginning of life" — even if it only became apparent later. By contrast, childhood schizophrenia, he contended, usually occurred only after "at least two years of essentially average development."

Kanner's emphasis on the inborn quality of the 11 children's traits was crucial to his assertion that he had discovered a new syndrome. As Silberman says, "Kanner needed this dichotomy so he could claim his own turf."

Kanner's gambit worked. His paper quickly established autism as a new condition, as well as a new field of study. It also cemented the idea that there are two types of autism, innate and regressive, distinguished by the different onsets and, presumably, different etiologies and developmental pathways. Researchers investigating childhood schizophrenia politely objected, noting that Kanner's 11 children sounded a lot like children they had studied. Later, during the 1950s, Kanner himself noted that the line between innate and regressive autism was fuzzy. But by then, Silberman notes, Kanner could afford this retreat because his reputation had been secured — and deservedly so.

In the meantime, the dichotomy stuck, and the vast literature that rose around it consistently classified autism as either innate or regressive. Although this sharp divide inspired valuable research, it also caused problems. In Kanner's day and after, he and other researchers, most notably Bruno Bettelheim, cited regression as evidence that **unaffectionate 'refrigerator' mothers** or working women could somehow warp their children's development. (Kanner eventually **retracted this view**.) More recently, anti-vaccine groups have pointed to regression, which frequently occurs at an age when children receive several vaccines, as proof that the shots can cause autism — **a spurious argument** that has contributed to outbreaks of measles (including a recent outbreak in Minnesota), whooping cough and other serious illnesses.

In fact, after 70 years of autism research, there is still no clear definition of what regression is. Psychologists **Brian Barger** and **Jonathan Campbell** have **wrestled with this problem** energetically over the past few years, combing through more than 100 studies. They have concluded that the literature on regression is "**without a central conception**" and has "no universally agreed-upon central definition."

In one meta-analysis of 85 papers, the pair uncovered a hodgepodge of definitions for virtually every type of regression commonly described in autism research — among them, language regression, social regression, motor regression, 'mixed' regression, 'regression, developmental,' just plain regression and even 'regression, unspecified.' In the case of language regression, for instance, they found no agreement on how many words a child must have had and then lost, or how long she needed to have used them, to qualify as having regressed. "You may have one paper saying it's a single word," Barger says, whereas another would require 20 words or the use of two- and three-word phrases. One lab might say the child must possess language skills for at least three months before losing them, but another might shorten that window to only a week.

Other definitions were similarly tangled. 'Social regression' referred to the loss of a varying subset of skills from a list including, but not limited to, emotional expressiveness, joint attention, eye contact, play skills and the child's response to her own name. Definitions of 'language-social regression' also included different mixes and measures of language and social-skill loss. 'Mixed regression' definitions encompassed losses of language, social ability or other skills — sometimes specified (such as motor), sometimes unspecified and sometimes hopelessly broad (such as 'developmental'). Possibly the most consistent definition, though hardly the most helpful, was for 'regression, unspecified,' which, of course, almost always went unspecified.

This definitional disaster, Barger and Campbell wrote in a paper last year, has created **a "literature marked by conflicting results."** Barger says it also helps to explain the huge variations seen in estimates of regression's prevalence. "If you don't have a clear sense of what you're looking for, then you can't clearly prove that what you're looking for looks the same across independent replications." The problem, in short, isn't like comparing apples and oranges; it's more like comparing apples, oranges, pineapples, spinach and chicken salad. It's little wonder Barger and Campbell concluded that "the research to date should be considered preliminary."

They and many others say that these sorts of definitional and measurement problems may mask regression's true prevalence. Regression may be the norm in children with autism, says Campbell, professor of psychology at the University of Kentucky. "I think you have operational definitional problems. You have measurement problems. And the phenomenon itself is difficult," he says. "[Regression] might be part of a larger, normal development process. Maybe it's not specific to autism; maybe there are more kids that go through losses and delays and spurts."

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Sally Ozonoff

Streetlights and tiny things:

One challenge in spotting autism's onset is what scientists call the streetlight effect: the human tendency to look for things where we can most easily see them (whatever's visible beneath the proverbial lamppost) even though what we seek may lie elsewhere, off in the proverbial dark.

In the case of regression, researchers and parents both tend to focus on language, which usually appears (and sometimes regresses) in the second year of life. But when they focus too much on this one ability, as important as it is, they may overlook or forget gains or losses made earlier in less noticeable areas, such as sensory and motor skills. “Most autism likely involves what we are currently calling regression,” says **Joseph Piven**, professor of psychiatry at the University of North Carolina at Chapel Hill. But he adds that it may occur before speech arises, and in areas other than language, where it is less likely to be spotted and “much harder to call.”

Piven and his colleagues **documented this blind spot** in a 2015 study. They assessed 210 infant siblings of children with autism (who are at **high risk of autism** themselves) and 98 babies from families with no history of autism. They took a number of developmental measures every few months, starting at age 6 months. They then used the children’s scores on several measures at the 24-month mark to sort them into four groups: a low-risk group showing no signs of autism, a high-risk group also showing no signs of autism, and two additional high-risk groups that they further categorized as ‘moderate’ or ‘severe’ based on the number and severity of their autism traits.

The study’s key finding was that at 6 months of age, the children who would later be diagnosed with autism showed subtle but distinctive sensory and motor characteristics that had gone unnoticed. These signs showed up in areas that standard autism screenings don’t assess, and most parents and even professionals might miss them in the absence of other difficulties. The Autism Observation Scale for Infants (AOSI), for instance — which focuses on eye gaze, visual tracking, imitation and other early social-communicative behaviors — picked up no significant differences among the four groups at 6 months. And at 12 months, this same screen detected subtler autism traits only in the group ultimately placed in the ‘severe’ group at 24 months.

As the researchers say, it would be premature to consider these newly recognized signs definitive harbingers of autism, because they might occur at lower rates in typical children as well, although the researchers did not assess that. The study wasn’t meant to generate diagnostic markers. But it does suggest that subtle signs of autism are there early on. “My take on this topic is that regression is a misnomer,” Piven says.

Other researchers have found that early social changes are also easily overlooked. In a 2011 study, Ozonoff and her colleagues watched home videos of children with regressive autism throughout their first two years, scoring them on four budding social skills: vocalizing, gazing at faces, sharing smiles and pointing as a way to direct another person’s attention. Reviewers attending to these behaviors noticed signs of social regression between 12 and 24 months of age in all of the children later diagnosed with autism, well before the children were diagnosed and before anyone noticed anything amiss. Parents and standard autism screens, such as the Autism Diagnostic Observation Schedule, missed these problems. In two-thirds of the children whose video histories showed some form of social regression, their parents had not picked up on it at the time.

The picture of regression may be even further complicated by some evidence that it occurs in typical children as well. A team led by Brignell and her colleague **Angela Morgan**, for instance, found that about one in seven typically developing toddlers at some point **regresses in eye gaze and in showing emotions**, compared with one in four children who have autism. A key difference, however, is that the children with autism are less likely than the typical children to make up for those losses. The researchers found that 26 percent of typically developing toddlers may also regress in other areas, such as eye gaze, social interest, or smiling or head movement in response to social stimulus, compared with 41 percent of children on the spectrum. “Loss,” Brignell says, “is not unique to autism spectrum disorder.”

Even with these regressive episodes, both typically developing children and those with autism usually gain skills in all these domains between their first and second years — though most toddlers with autism make their gains more slowly.

“Most autism likely involves what we are currently calling regression.” Joseph Piven

In hindsight:

A final but central problem in the regression literature is its heavy reliance on retrospective studies — those that depend on reconstructing events, rather than observing them as they occur. In these studies, researchers ask parents of a child who’s already been diagnosed or evaluated for autism to remember their child’s development, highlighting any noticeable loss of skills. If the parents recall a typical course of development that suddenly hit a snag, the researchers might deem the child’s autism onset regressive. It’s only during the past decade or so that Ozonoff and others have used prospective studies or home videos to check parent recall. Their work has shown that parents’ memories, like most human memories, can be astoundingly unreliable.

People tend to misremember things such that they fit their current impressions or beliefs — a form of confirmation bias. As a result, they may remember a troublesome teen as a more ornery toddler than she really was, or forget that an agreeable 10-year-old was, at 2, impossibly impossible. Asking parents to remember the progress of a child showing signs of autism is especially perilous. Along with the difficulty of noticing subtle setbacks (of the sort even researchers miss), these faint cues are also more likely to be forgotten. Compounding the problem, classic recall exercises can easily steer a parent’s memory toward her child’s biggest, most memorable lapses, creating the illusion of a sudden regression.

This illusion may be further magnified by something called the telescoping effect: The more time that passes after a significant event occurs, the more likely a person is, in remembering that event, to move it forward in time. That is, memory draws distant events closer, like a telescope focused on a distant object.

A 2011 study by University of California, San Francisco researcher **Vanessa H. Bal** is one of several that show how telescoping encourages a false perception of regression. Bal found that in those instances when children had acquired and then lost skills, parents remembered **both the appearance and the disappearance** of those skills as happening later — and nearer to the present — than records showed. Those errors grew in proportion to the amount of time that had passed between event and recall. The parents of an 18-month-old, for example, might accurately remember the appearance of a trait at 13 months. But three years later, they might place that milestone at 18 or 20 months. This telescope effect may have helped to set the purported average age of regression at 18 to 20 months in most studies.

Ozonoff is now working on a paper she calls, tongue half in cheek, “Everyone regresses.” Her point is not to say that late regression never occurs, but that an overemphasis on the division between supposedly innate and seemingly regressive autism is a red herring and a distraction. A better approach, she says, is to think instead of multiple factors that could generate a kaleidoscopic range of onsets. “I don’t think of onset as two or four categories,” she says. “There’s not many different things, but one thing that looks different in different cases.”

Early overgrowth in the brains of children with autism could **explain this diversity**. A small 2001 study found that in children with autism, **the brain appeared to grow abnormally fast** up to 24 months. Later, the brains of these children appear to undergo synaptic pruning — a process that trims back connections among neurons — at faster rates than is seen in typical children. (Many other studies have found that children with autism **have too many synapses**, rather than too few.)

In 2015, the late neuroscientist **Annette Karmiloff-Smith** published a paper consolidating this and other findings into an **‘over-pruning’ hypothesis** of onset: Too much growth, followed by too much cutting back, leads to the appearance of autism traits.

Less than two years later, Piven reported that the timing of the overgrowth coincides with the middle of the second year, when social and language problems often appear. When Piven’s team closely examined a series of structural brain scans of 15 children diagnosed with autism, they found a **pattern of overgrowth in the children’s brains** between 6 and 12 months of age, even in children who did not show any autism traits until around 18 months. This finding nicely supports the idea — key to the over-pruning hypothesis — that behavioral regression appearing in the second year arises from atypical processes that start in early infancy or even before birth.

Karmiloff-Smith and others have suggested that ongoing atypical development gradually generates enough atypical brain activity to overwhelm the processes driving typical behavior — so that eventually a typically developing circuit, having produced a behavior such as early speech, loses the ability to do so. The seemingly sudden loss is actually long in the making.

The idea “fits perfectly well” with a leading theory of dynamic brain development, says **Kevin Mitchell**, a neurodevelopmental geneticist at Trinity College Dublin in Ireland. According to this dynamic or ‘neuroconstructivist’ theory, **articulated with particular force** by Karmiloff-Smith, atypical outcomes such as autism come about not simply because of major genetic faults or distinct environmental insults, but from an aberrant unfolding of complex neurodevelopmental processes. Over time, these processes create the differences, bad and good, that distinguish all of us; in the case of autism, they may simply create differences that are more noticeable and consequential.

Setting aside Kanner’s innate/regressive dichotomy would open up rich theoretical and experimental terrain for exploring this theory. And it might offer more immediate returns as well. If clinicians recognize that autism typically appears gradually rather than abruptly and learn to spot the signs earlier, they will have more opportunity to help the child and to meet the challenges that atypical development can present. Pediatricians might even start measuring social and perhaps motor skills at routine well-child visits — something, Ozonoff says, that “would require all of us, parents and providers, to think of how autism emerges in a fundamentally different way.” A more dynamic, multifaceted view of brain development might not only be more useful, she notes, it’s also more likely to be true.