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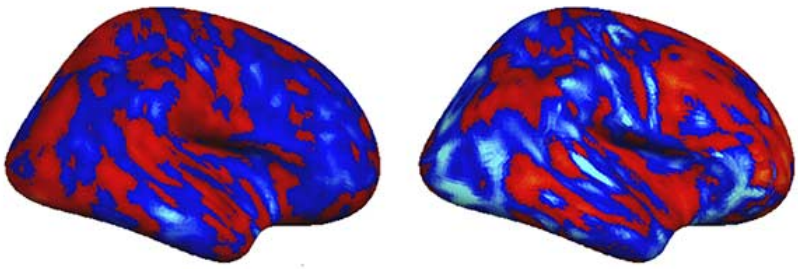
Noisy patterns of connectivity mark autism brains

Alla Katsnelson
29 January 2015



Clear connection: The more similar an individual's connectivity pattern is to that of controls (blue and red), the milder his or her autism symptoms.

A new study may have solved a decade-old debate about whether the brains of people with autism are more or less connected than those of controls: They're both, depending on where in the brain you look. The study, published 19 January in *Nature Neuroscience*, suggests that a mix of abnormally strong and weak brain connections is a hallmark of the disorder[1].

"In the very same individual, we can see both, depending on spatial distribution," says Marlene Behrmann, professor of psychology at Carnegie Mellon University in Pittsburgh.

Behrmann and her colleagues analyzed functional magnetic resonance imaging (fMRI) scans from 68 adults with high-functioning autism and 73 age-matched controls. As a group, people with autism showed the opposite pattern of connectivity to that seen in controls.

"Those areas that are typically highly connected were less connected in [the autism group], and those areas that are typically less connected were more connected in the autism group," says Behrmann.

On an individual level, however, the researchers found noisier patterns of connectivity in the brains of people with autism than in controls. The more these patterns deviate from those of controls, the more severe a person's autism symptoms tend to be.

The findings jibe with previous studies from Behrmann's team, which suggest that signaling in the brains of people with autism is more variable than in controls. They may also help to reconcile discrepant findings on brain connectivity that have dogged autism researchers for years.

"They're actually saying that maybe everyone with [autism] is just different from that canonical response or pattern of brain activity," says Dan Kennedy, assistant professor of psychological and brain sciences at Indiana University in Bloomington, who was not involved in the work.

The findings also fit with the growing appreciation of autism's heterogeneity. "We know there are lots of different causes of autism and different developmental trajectories," says Kennedy. "To expect that everyone with autism is going to show some clear biological commonality might be incorrect."

Parsing patterns:

Most previous studies of brain connectivity in autism had smaller sample sizes and focused on a select

few regions of the brain. In the new study, Behrmann and her colleagues analyzed data from the Autism Brain Imaging Data Exchange (ABIDE), an open-access repository of more than 1,000 fMRI scans from 17 labs worldwide.

They measured connectivity by mapping the level of synchrony between different brain areas across and within the two hemispheres of the brain. Two areas are considered connected when they light up on the scans simultaneously.

Overall, connections that are strong in controls are weaker in people with autism and vice versa. But these group-level differences do not hold up when the researchers look at individual connectivity patterns, which vary widely within the autism group. This idiosyncrasy tracks with autism severity, so that individuals whose brain connectivity is most different from that of controls score highest on the Autism Diagnostic Observation Schedule, a widely used scale for assessing autism.

Some experts say this should come as no surprise. “We do know that regardless of the psychiatric disorder studied, there’s always more variability in patient groups,” says Vinod Menon, professor of psychiatry and behavioral sciences at Stanford University in California, who was not involved in the work.

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- Imaging studies question connectivity theory of autism

Others say the findings highlight a new way of thinking about altered brain connectivity in autism. “If it’s confirmed, it brings up a very new avenue of research,” says Adriana Di Martino, assistant professor of child and adolescent psychiatry at New York University’s Langone Medical Center. Di Martino was not involved with the study but manages the ABIDE database.

Di Martino and her colleagues also found evidence for both over- and underconnectivity in the brains of people with autism in a 2013 analysis of 763 scans from ABIDE. But their work differed in that it focused on specific brain circuits and contained a more diverse pool of participants, including children.

Expanding the new study to include children will clarify whether noisy connectivity is a cause or effect of autism, according to Menon. “Mapping out the developmental trajectory of these changes is, I think, going to be an interesting and important action for the future,” he says.

Behrmann says she plans to study children and hopes other labs will extend the study to people with severe autism.

“The more the field can work together to aggregate big datasets,” she says, “it’s my opinion that we will be able to uncover patterns that have heretofore been elusive.”

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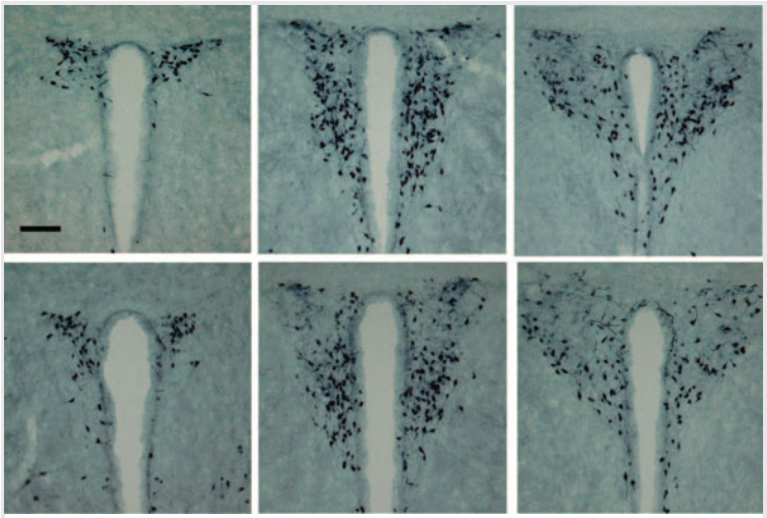
Mouse study bolsters case for oxytocin in autism

Jessica Wright
2 February 2015



Short supply: Mice missing the autism-linked gene CNTNAP2 (bottom) have fewer neurons that produce oxytocin than do controls (top).

Oxytocin has been tenuously tied to trust, monogamy and a slew of other social behaviors. It has also long been eyed as a treatment for autism, but trials in people with the disorder have yielded conflicting results. A new study, published 21 January in *Science Translational Medicine*, bolsters the case for the so-called 'trust hormone' as an autism therapy, finding that it eases social deficits in a mouse model of the disorder[1].

"There is no drug approved for treating social deficits [in autism]," says Olga Peñagarikano, assistant researcher in Daniel Geschwind's lab at the University of California, Los Angeles. "We don't think oxytocin is going to be effective in everybody, but I think it will be very interesting to find a way to determine [who] could benefit."

The study is the first to rigorously examine the effects of oxytocin treatment in an autism model, in this case mice lacking the CNTNAP2 gene. The mice show little interest in other mice, a social deficit reminiscent of those seen in autism. But 30 minutes after a single injection of oxytocin, the mice approach others in their cage.

The mice also have low brain levels of oxytocin, suggesting that people who have autism and mutations in CNTNAP2 have a similar deficit — and may similarly respond to oxytocin treatment.

"This paper is exciting, because they're looking at a potential therapeutic agent — in this case oxytocin — which is already being tested in human beings," says Robert Malenka, professor of psychiatry and behavioral sciences at Stanford University in California. "We can start delving into the detailed mechanisms [in mice] in ways you can't do in [people]."

Social drug:

CNTNAP2 emerged as an autism gene in 2006, after researchers found inherited mutations in both copies of the gene in a group of Amish children with the disorder[2]. It then quickly grew to prominence as an autism gene, and the mouse model became popular in autism labs, including for tests of autism drugs[3]. However, a study published last week hints that the gene's link to autism may be limited to

inherited mutations in both copies of the gene[4].

In the new study, the researchers used young mice to test five drugs known to affect social behavior. A single injection of either oxytocin or vasopressin eases social deficits, they found. Further experiments revealed that vasopressin in fact acts through the oxytocin pathway.

The most intriguing finding is that oxytocin has no effect on social behavior in control mice, says Peñagarikano. The mutant mice have fewer neurons that make oxytocin and low levels of the hormone in the brain. No other mouse models of autism — except for mice that model the related fragile X syndrome — have shown this pattern[5].

“CNTNAP2 doesn’t represent all of autism, but it’s one little slice,” says Larry Young, professor of psychiatry at Emory University in Atlanta, who was not involved with the study. “This points to the fact that in some slices of autism, oxytocin is not affected at all and stimulating the oxytocin system won’t have an effect. In other slices, it will.”

To directly link the improved social behavior to oxytocin in the brain, the researchers stimulated the hormone’s release in two other ways: injecting a drug called melanocortin that stimulates oxytocin release and using artificial receptors, called DREADDS, to activate oxytocin neurons. Both methods improved social functioning.

In traditional approaches, “no one even knows if oxytocin gets into the brain or if it leads to effects through some other weird way,” says Robert Froemke, assistant professor of physiology and neuroscience at New York University, who was not involved in the study. “The use of DREADDS to engage the oxytocin system is a major advance.”

To test the effects of long-term oxytocin treatment, the researchers injected mouse pups with oxytocin every day between 7 and 21 days of age, when the mice wean from their mothers. Nine days after stopping the treatment, the mice continue to show a boost in brain levels of oxytocin and improvements in social behavior. “It would be very interesting to see how long this effect lasts,” says Peñagarikano.

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She and her colleagues plan to test whether oxytocin has the same effect on adult mice. “Maybe there’s a developmental window that would be optimal for treatment,” she says.

These and other experiments may reveal exactly how oxytocin affects the brain long term, notes Sue Carter, professor of biology at Indiana University in Bloomington, who was not involved with the study. “If you understand the mechanism, then you can use it to inform treatment rather than just giving something and hoping it won't have adverse effects.”

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Julia Yellow

Spotted: Video therapy; supplement slam

By Katie Moisse

30 January 2015

Welcome to Spotted — a weekly roundup of autism papers you may have missed and media mentions you should know about.

We scour the scientific literature and the press daily for all things autism. With Spotted, what's on our radar is also on yours.

Here's what's out there this week:

Home videos

A small study published in *The Lancet Psychiatry* suggests that a video-based therapy may ease autism symptoms in 'baby sibs' — infants who have a brother or sister with the disorder and a 20-fold increased risk of developing it themselves. Researchers used home videos to help parents learn and adapt to their baby's style of communication. After five months, the baby sibs were more attentive and socially engaged than baby sibs who didn't get the therapy — a promising result, albeit preliminary. "Targeting the earliest risk markers of autism, such as lack of attention or reduced social interest or engagement, during the first year of life may lessen the development of these symptoms later," lead researcher Jonathan Green, professor of child and adolescent psychiatry at the University of Manchester in the U.K., told *Reuters*.

Supplement slam

The Federal Trade Commission (FTC) has reprimanded a supplement manufacturer for suggesting that its capsules and syrups can ward off symptoms of autism. The company, called NourishLife, makes 'Speak' — a line of omega-3-based supplements touted as treating the communication deficits associated with autism. The FTC ordered the company to alert its customers that the claims "aren't backed by scientific evidence." This isn't the first time a supplement maker has overstepped, but it's unique in that NourishLife was in cahoots with a now-deactivated website claiming to be an "independent, objective resource for research or other scientific information," according to the FTC filing (h/t @virginiahughes).

Tracking technology

Two long articles in *The New Yorker* spotlight new technologies aimed at tracking autism behaviors. One system, called Affectiva, measures “the distribution of wrinkles around an eye, or the furrow of a brow,” to capture emotional expressions on the face. The other, called LENA, uses voice recognition software to track communication between children and caregivers. Both systems are being tested in children with autism with hopes that they’ll recognize — and even predict — certain behaviors. We’ve covered these sorts of technologies before and will bring you the latest on wearable tech’s promise for autism next week.

Making connections

The National Institutes of Health has launched a new Down syndrome resource called DS-Connect, an online registry that links families, researchers and advocacy groups. Clinicians can use the registry to access de-identified study data and learn more about the needs and characteristics of people with Down syndrome. Some 2,700 families have registered so far — a significant step toward the agency’s goal of 10,000. An estimated 38 percent of people with Down syndrome also meet the criteria for autism.

Food as ‘death sentence’

An article in *The New York Times* takes a sobering look at Prader-Willi syndrome, an autism-linked disorder marked by incessant hunger and obesity. “I think the problem with most people’s perception of Prader-Willi is: It’s just a fat kid,” says Peter Girard, whose son Jeremy had the disorder and died from a ruptured stomach after overeating. “They don’t understand that food is a death sentence to these kids.”

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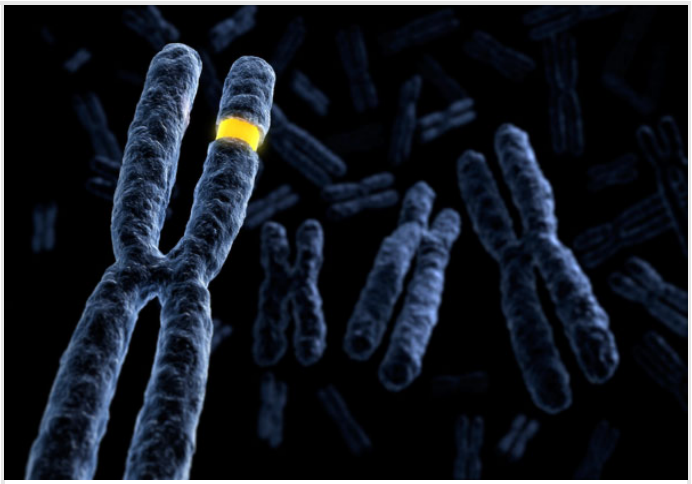
New database matches mutations with potential effects

Marissa Fessenden
28 January 2015



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Dose matters: DNA duplications and deletions, called copy number variations, are associated with autism.

A new tool helps predict whether large DNA duplications and deletions, common among people with autism, are harmful or benign, reports a study published 18 December in *Genetics in Medicine*[1].

So-called copy number variations (CNVs) are often associated with conditions such as autism but are also seen in unaffected individuals. The exact composition of a CNV can vary from person to person, making it difficult to discern its effects on gene expression.

The new tool, called Scripps Genome Annotation and Distributed Variant Interpretation Server, or SG-ADVISER, matches CNVs against a database of known genetic variants linked to various disorders. It consists of a Web server that collects genomic data, a computing system that scours databases for known variants and a user interface. It can analyze a complete genome in an average of six minutes.

Researchers tested the tool on 10 genomes from the Scripps Wellderly Genome Resource — a database of elderly people's genomes created to enable study of the genetics of a healthy lifespan — and found that each genome contains an average of 3,782 CNVs. They then applied the tool to a panel of CNVs culled from microarray data, which include 5,104 'pathogenic' CNVs implicated in a range of disorders and 5,822 'harmless' CNVs with no known effects. The tool accurately identified the harmful variants 94 percent of the time.

The tool can also predict whether newly discovered CNVs are harmful — a function the researchers tested by screening the known variants, but first disabling the system that checks the database for those variants' associations. In this mode, the tool correctly identified 90 percent of the harmful variants.

The tool can be used by those with no bioinformatics expertise, according to the researchers, and is freely available online. They plan to develop a version that can be used to study CNVs in mice.

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Autism as a disorder of prediction in a 'magical' world

By Pawan Sinha, Margaret Kjelgaard and Annie Cardinaux
3 February 2015

Margaret Kjelgaard

As I sit in my kitchen, trying to organize my thoughts for this piece, I'm thoroughly distracted by my son, pacing in the hallway, repeatedly asking for "More pig cow! More pig cow!"

A small plastic pig and cow have become his latest 'transitional objects' — the things he must carry 24 hours a day to feel complete. The exact objects vary over time. It was a pair of pink crocs a few weeks ago; now it is farm animals.

What does not change in my family is that every morning starts with all of us searching his bed, his room and the house to find the objects so that we can get our day started with some semblance of normalcy. He simply cannot get on his school bus without his objects. He is 9 years old and he has autism.

Trained as a psycholinguist and studying autism in the 1990s, I focused on how higher-order linguistic processes are different in children with autism than in typically developing children. On some level, it was frustrating that theories of autism didn't seem to encompass the reality of autism as we knew it clinically.

Autism was a compendium of seemingly disparate symptoms. It seemed that the theories of autism at that time accounted only for distinct yet unrelated pieces of the puzzle. How did deficits in theory of mind — the ability to understand others' thoughts or feelings — account for restricted interests, repetitive behaviors or sensory issues?

-Margaret Kjelgaard

In a paper published last year, we presented a theory that might help explain some of autism's diversity of traits: Autism's salient traits may be manifestations of an impairment in the ability to predict what might happen next[1].

Our initial inspirations for this theory came from accounts, similar to our own, of people with autism and their parents. Although subjective, these descriptions embody knowledge borne out of years of experiencing and observing autism at close range. Even though personal accounts might not provide answers, they point to the big questions.

Many caregivers of children with autism note that these children require a structured, highly predictable environment. Even slight deviations from such predictability can prove distressing.

We informally refer to our proposal as the 'magical world' theory of autism. The hallmark of magic is the element of surprise, an unpredicted outcome. In small doses, such performances are enjoyable. Our theory posits that for an individual with autism, however, too much of the world has this characteristic, and events transpire without forewarning or apparent cause.

Our predictive skills are what allow us to fruitfully interact with our environment and interpret observations in the context of what has transpired before. Without these skills, the world is likely to appear chaotic.

This seemingly capricious environment induces anxiety, the feeling of a loss of control and, overall, a sense of being overwhelmed. Attempts to interact with the world, or to interpret it, will be devoid of the modulatory effects of prior context.

Central theory

Autism is famously heterogeneous in the way it manifests in different people. But, even within a single individual, it affects a remarkably diverse range of functions, such as motor skills, language and social behavior. It may well be that this diversity is the result of a constellation of disparate causes. But we cannot rule out the alternative possibility: Seemingly unrelated traits might have shared underpinnings.

As we considered the prediction theory further, we identified ways in which it could account for these seemingly disparate traits of autism. For instance, communication and social interactions require learning how one event predicts another — even when this predictive relationship is weak.

My son was my second child and he was a bit different from my first. He wasn't hitting his milestones on time. I found myself lying to the other parents at the playground about his age when he wasn't walking at 15 months, "Oh, he's just a really big 1-year-old!"

As the months passed, it became increasingly difficult to ignore the signs. On his second birthday, I called early intervention and after the hearing and vision tests, went for a diagnosis.

From that moment forward, my thinking about autism was forever changed.

I stopped caring so much about abstract and hypothetical questions regarding differences in linguistic minutiae between typically developing children and those with autism. There was a more basic issue I needed to grapple with: Why is life so difficult for my son?

Like every parent who has a child with autism, I have tried to make sense of the many ways in which my son is 'different.' Why does he not speak? Why is he so insistent on rituals? Why doesn't he play with others? Why is he so averse to sounds? The list goes on.

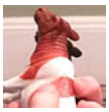
The answers in the field have often seemed ad hoc, targeted to this or that trait. Maybe that is the best we can do; a cohesive account simply may not exist. But it seems too early to give up the search.

- M.K.

A shrug of the shoulders and lowered tone suggest the imminent end of a conversation; a sideways glance suggests boredom. Tolerating and tuning out background sounds, such as the rhythmic hum of a fan, requires predictive abilities as well.

Similarly, studies of stress and sensory bombardment have shown that repetitive behaviors may emerge as compensatory responses to a seemingly unpredictable environment. As a result, difficulties in social interactions and a tendency to engage in repetitive behaviors — although superficially unrelated — could be manifestations of a common underlying problem in prediction.

Experimental support



As a scientist, I appreciate the research road map that the 'magical world' account provides.

As a mom, I turn to it to help me understand some of the mystery of my son's joys and frustrations, and to improve his quality of life.

- M.K.

We are not only reexamining existing experimental evidence through the prism of our theory, we are designing studies to test it. In our lab at the Massachusetts Institute of Technology, we are testing the prediction theory in the context of sensory hypersensitivities.

Our theory is that low predictive skills may lessen habituation to repeated patterns and so render them aversive. We have begun several studies to measure habituation response to either predictable or unpredictable sequences of stimuli, such as sounds and simple or more naturalistic visual stimuli. We are also investigating motor tasks that stress prediction, such as trying to track objects as they move in a computer game, as well as the motion of objects in more natural environments.

We hope that others will also continue to subject the theory to further tests — in particular, to assess whether people with autism have different predictive skills than do typical individuals or those with other developmental delays.

It is also exciting to note that other labs are beginning to make the case for the involvement of predictive impairments in autism. For instance, researchers have proposed a Bayesian account of autism: Experience exerts a weaker influence for people with autism than it does for neurotypical individuals[2].

Some researchers have suggested that environmental uncertainty may pose challenges to the autistic brain[3] and a possible connection between hypersensitivity and reduced prediction[4]. These accounts germinated independently, but we hope that an exchange of ideas will help further their development.

The magical world theory is an attempt to find a common thread across distinct aspects of autism. But even as we are encouraged by how well it fits with data and anecdotes, we have to acknowledge that — like any scientific theory — it may well be wrong.

Perhaps autism truly is a constellation of many separate traits, each with its own distinct cause. But the overarching principle of parsimony — which has served science so well — argues for exploring possible commonalities of cause.

If the theory of predictive impairment in autism proves to have merit, it would have great relevance for strengthening autism diagnosis and designing therapies. Even if it turns out to be incorrect, the data we will gather along the way will help us better understand the true nature of this complex condition — and a little of the mystery behind the magical world of autism.

Pawan Sinha is professor of vision and computational neuroscience at the Massachusetts Institute of Technology. Annie Cardinaux is a technical associate in his laboratory. Margaret Kjelgaard is associate professor of communications sciences and disorders at Massachusetts General Hospital Institute of Health Professions.

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Wearable sensors aim to capture autism in action

Kate Yandell
30 January 2015

Wearable devices can now measure everything from steps walked to calories burned and even how peacefully a person sleeps. The utility of these ubiquitous gadgets may soon extend beyond tracking wellness goals to recording complex behaviors in people with autism.

Researchers in Boston and Atlanta are enlisting the help of 20 families to test various monitoring technologies in their homes for a month, while a New York-based group is testing similar technologies in smaller pilot groups.

Voice recorders, for instance, can quantify how much and in what way a child is interacting with other people. Physiological data, such as heart rate and sweat levels, may predict when a child is about to engage in aggressive or self-harming behavior.

Data from these automated biosensors could be far more standardized than current measures of behavior, which rely on caregivers to classify incidents and remember to record them. But making automated, round-the-clock behavioral recording a reality will require substantial work, suggests a review published in the 2014 *IEEE Engineering in Medicine and Biology Society Conference Proceedings*.

For one thing, wearable devices must be comfortable and easy to use. They must also be sensitive and specific enough to detect subtle behaviors in unpredictable environments, such as homes or schools.

Some researchers, such as Matthew Goodwin, hope to go one step further and predict autism behaviors before they occur. For five years, Goodwin and his collaborators have been testing the Q-sensor — a wrist device that measures skin surface temperature and other physiological characteristics — at about a dozen sites. Goodwin's team is analyzing the data to link signs of stress to problematic behaviors, with the ultimate goal of finding predictors of the behaviors.

Goodwin, assistant professor of health sciences at Northeastern University in Boston, is also collaborating with researchers at the Georgia Institute of Technology to monitor 20 children with autism in their homes. The researchers have spent the past year working to optimize in-home video monitoring systems, tablet and computer interfaces for caregivers to operate the cameras and timestamp behaviors, and wearable sensors to track the children's movement, sweat, temperature and sleep.

His team is also working with Catherine Lord to test a wearable voice-recognition system called LENA to monitor how children with autism vocalize and engage verbally with others. The researchers plan to use the tool in conjunction

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with the Q-sensor and notes on behavior from parents. But LENA is finicky, sometimes mistaking the sounds of videogames for children's voices, or the sounds of children's voices for adult voices.

The researchers say they hope the setup will aid in designing and assessing treatments for children with autism. Their goal is to eventually track behavior with the same rigor and objectivity now used to map the genetics of autism. For now, however, they aim to focus on finding user-friendly technology, overcoming technical bugs and, perhaps most importantly, figuring out which measurements best signal clinically relevant behaviors.

autism diagnosis, treatment
- Matthew Goodwin: Bridging disciplines for autism care
- Inconsistency plagues studies of parent-mediated therapies
- Video game device detects repetitive behavior

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Science's gender gap tied to beliefs about brilliance

Jennifer Richler
27 January 2015

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The underrepresentation of women in science has sparked much discussion and debate in the past few years. Explanations for the discrepancy invoke everything from women's unwillingness to work long hours and men's aptitude for abstract thinking to — most controversially — women's intellectual inferiority. But a new study, published 16 January in *Science*, suggests that mistaken beliefs about brilliance are the real culprit.

The researchers asked 1,820 faculty, postdocs and graduate students from 30 disciplines spanning the natural sciences, the social sciences and the humanities about the importance of innate intelligence and raw talent in their fields.

The relationship they found was striking: The more a field emphasized the importance of giftedness, the greater its gender gap. The researchers suggest that these 'field-specific ability beliefs' conspire with long-held gender stereotypes, which associate only men with natural intellectual ability.

"Consider how difficult it is to think of even a single pop-culture portrayal of a woman who displays that same special spark of innate, unspooled genius as Sherlock Holmes," Sarah-Jane Leslie, professor of philosophy at Princeton University and one of the researchers on the study, said in a teleconference. Girls or women presented as smart are typically shown to be extremely hardworking, she added, citing "Harry Potter's" Hermione Granger as an example.

Beliefs about the importance of raw talent also predict the underrepresentation of African-Americans, who, like women, evoke negative stereotypes about intelligence. This relationship doesn't hold for Asian-Americans, however, perhaps because Asian-Americans aren't stereotyped as having inferior intelligence, the researchers say.

To address competing hypotheses, the researchers also asked participants about their discipline's work demands, the proportion of students admitted to a graduate program each year from the pool of applicants, and the emphasis on abstract thinking. (Some studies suggest that men and, incidentally, individuals with high-functioning autism, are superior abstract thinkers.)

None of these variables predict the gender gaps across disciplines. In fact, fields that are more selective in their admissions process tend to have a greater representation of women. Although this trend doesn't reach statistical significance, it joins other studies in refuting claims about the purported inferior intellect of women.

Related content:

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If the lack of women in many scientific disciplines truly comes down to an emphasis on the importance of brilliance, then there might be an easy fix. The researchers suggest that these disciplines could retool their message to deemphasize raw ability. It's not a perfect solution, but changing the way we communicate is surely faster than changing stereotypes about gender and intelligence.

science
- Women researchers in autism face glass ceiling
- Study on 'extreme male brain' theory of autism draws critics

We might also look to disciplines relevant to autism research, such as molecular biology and biochemistry, for solutions. These particular fields were outliers in the study, found to emphasize raw talent while also including relatively high proportions of women, in contrast to most scientific disciplines. Perhaps these fields impart a more inclusive message to prospective colleagues. If so, they could become models for others to emulate.

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