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AI face-scanning app spots signs of rare genetic disorders

Deep-learning algorithm helps to diagnose conditions that aren't readily apparent to doctors or researchers.

Elie Dolgin

A deep-learning algorithm is helping doctors and researchers to pinpoint a range of rare genetic disorders by analysing pictures of people's faces.

In a paper[1] published on 7 January in *Nature Medicine*, researchers describe the technology behind the diagnostic aid, a smartphone app called Face2Gene. It relies on machine-learning algorithms and brain-like neural networks to classify distinctive facial features in photos of people with congenital and neurodevelopmental disorders. Using the patterns that it infers from the pictures, the model homes in on possible diagnoses and provides a list of likely options.

Researchers are improving the ability of algorithms to help spot the physical characteristics of conditions such as Cornelia de Lange syndrome. **Michael Ares/The Palm Beach Post via ZUMA**

Doctors have been using the technology as an aid, even though it's not intended to provide definitive diagnoses. But it does raise a number of ethical and legal concerns, say researchers. These include ethnic bias in training data sets and the commercial fragmentation of databases, both of which could limit the reach of the diagnostic tool.

Researchers at FDNA, a digital-health company in Boston, Massachusetts, first trained the artificial intelligence (AI) system to distinguish Cornelia de Lange syndrome and Angelman syndrome — two conditions with distinct facial features — from other similar conditions. They also taught the model to classify different genetic forms of a third disorder known as Noonan syndrome.

Then the researchers, led by FDNA chief technology officer Yaron Gurovich, fed the algorithm more than 17,000 images of diagnosed cases spanning 216 distinct syndromes. When presented with new images of people's faces, the app's best diagnostic guess was correct in about 65% of cases. And when considering multiple predictions, Face2Gene's top-ten list contained the right diagnosis about 90% of the time.

Narrowing the field

Eventually, FDNA wants to develop this technology to help other companies filter, prioritize and interpret genetic variants of unknown significance during DNA analysis. But to train its models, FDNA needs data.

So the Face2Gene app is currently available for free to healthcare professionals, many of whom use the system as a kind of second opinion for diagnosing rarely seen genetic disorders, says study co-author Karen Gripp, a medical geneticist at the Nemours/Alfred I. duPont Hospital for Children in Wilmington, Delaware. It can also provide a starting point in cases in which a doctor doesn't know what to make of a patient's symptoms. "It's like a Google search," Gripp says.

Gripp, who is also FDNA's chief medical officer, used the algorithm to help diagnose Wiedemann–Steiner syndrome in a young girl she treated last August. Although a little short for her age, the four-year-old didn't have many of the syndrome's distinguishing physical features, other than the fact she had lost most of her baby teeth and several adult teeth were already coming in.

Gripp had read case reports describing premature dental growth in children with Wiedemann–Steiner syndrome, an exceedingly rare disorder caused by mutations in a gene called *KMT2A*. To shore up confidence in the diagnosis, Gripp uploaded a photo of her young

patient to Face2Gene. Wiedemann–Steiner syndrome appeared among the software's top hits.

Gripp subsequently confirmed the girl's diagnosis with a targeted DNA test. But she says that the AI approach helped her to narrow down the possibilities and saved the cost of more expensive multi-gene panel testing.

'Killing it'

The program's accuracy has improved slightly as more healthcare professionals upload patient photos to the app, says Gurovich. There are now some 150,000 images in its database.

And in an unofficial comparison conducted between Face2Gene and clinicians last August at a workshop on birth defects, the program outperformed the people. Charles Schwartz, a geneticist at the Greenwood Genetic Center in Greenwood, South Carolina, distributed facial pictures of ten children with "fairly recognizable" syndromes and asked attendees to come up with the correct diagnoses.

In only two instances did more than 50% of the 49 participating clinical geneticists pick the right syndrome. Face2Gene made the right call for seven of the pictures.

"We failed miserably, and Face2Gene killed it," says Paul Kruszka, a clinical geneticist at the US National Human Genome Research Institute in Bethesda, Maryland. Soon, he says, "I think every paediatrician and geneticist will have an app like this and will use it just like their stethoscope".

Silos and bias

But the algorithm is only as good as its training data set — and there's a risk, especially where rare disorders that affect only small numbers of people worldwide are concerned, that companies and researchers will begin to silo and commodify their data sets. "That threatens the main potential good of this technology," says Christoffer Nellåker, a computational biologist at the University of Oxford, UK, who has spearheaded efforts to facilitate data-sharing in this field.

And ethnic bias in training data sets that contain mostly Caucasian faces remains a concern. A 2017 study[2] of children with an intellectual disability found that whereas Face2Gene's recognition rate for Down syndrome was 80% among white Belgian children, it was just 37% for black Congolese children. With a more-diverse training data set, however, the algorithm's accuracy for African faces improved, showing that more-equitable representation of diverse populations is achievable.

"We know this problem needs to be addressed," says Gurovich, "and as we move forward we're able to have less and less bias."

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Rising drug prices linked to older products, not just newer, better medications

New drugs entering the market drive up prices, but drug companies are also hiking prices on older drugs

PITTSBURGH - It's no secret that drug prices are increasing, but to what extent are rising costs explained by the advent of newer, better drugs? A study from the University of Pittsburgh found that new drugs entering the market do drive up prices, but drug companies are also hiking prices on older drugs.

The paper, published in the January issue of Health Affairs, shows that for specialty and generic drugs, new product entry accounted for most of the rising costs, whereas for brand-name drugs, existing products explained most of the cost increases.

"It makes sense to pay more for new drugs because sometimes new drugs are more effective, safer or treat a new disease you didn't have a treatment for. Sometimes new drugs do bring more value," said lead author Inmaculada Hernandez, Ph.D., assistant professor at the Pitt School of Pharmacy. "But the high year-over-year increases in costs of existing products do not reflect improved value."

The researchers examined the list price of tens of thousands of drug codes from a national database between 2005 and 2016 and UPMC Health Plan pharmacy claims over the same time period. Drugs were considered "new" for the first three years they were available, or in the case of generics, the first three years after patent expiration.

What they saw was that each year the price of brand-name oral medications increased by about 9 percent - nearly five times the rate of general inflation over the same time period - and the price of brand-name injectables increased by 15 percent. In both cases, soaring prices were overwhelmingly attributable to existing drugs.

For instance, the list price for Sanofi's Lantus brand insulin increased by 49 percent in 2014. Lantus had been on the market for more than a decade.

"These types of insulin have been around for a while," Hernandez said. "Whereas the original patent for Lantus expired in 2015, dozens of secondary patents prevent competition, and it is this lack of competition that allows manufacturers to keep increasing prices much faster than inflation."

Specialty drugs saw steep price increases as well - 21 percent for oral and 13 percent for injectable - but in this case, new drugs were driving up the cost. Likewise, generics rose by 4 percent and 7 percent.

Additional authors on the study include Chester B. Good, M.D., M.P.H., and Natasha Parekh, M.D., M.S., and William Shrank, M.D., M.S.H.S., from the UPMC Health Plan; Walid Gellad, M.D., M.P.H., from Pitt, and David Cutler, Ph.D., from Harvard.

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Dog breeds really do have distinct personalities—and they're rooted in DNA

Most comprehensive study shows that distinct breed traits are actually rooted in a dog's genes

By Elizabeth Pennisi Jan. 7, 2019 , 1:00 PM

American Kennel Club descriptions of dog breeds can read like online dating profiles: The border collie is a workaholic; the German shepherd will put its life on the line for loved ones. Now, in the most comprehensive study of its kind to date, scientists have shown that such distinct breed traits are actually rooted in a dog's genes. The findings may shed light on human behaviors as well.

"It's a huge advance," says Elaine Ostrander, a mammalian geneticist at the National Human Genome Research Institute in Bethesda, Maryland, who was not involved with the work. "It's a finite number of genes, and a lot of them do make sense."

When the dog genome was sequenced in 2005, scientists thought they would quickly be able to pin down the genes that give every breed its hallmark personality. But they found so much variation even within a breed that they could never study enough dogs to get meaningful results.

So in the new study, Evan MacLean, a comparative psychologist at the University of Arizona in Tucson, Noah Snyder-Mackler at the University of Washington in Seattle, and colleagues began by looking at behavioral data for about 14,000 dogs from 101 breeds. The analyses come from the Canine Behavioral Assessment & Research Questionnaire (C-BARQ), a sort of pet personality quiz developed by James Serpell, an ethologist at the University of Pennsylvania. C-BARQ asks questions like, "What does your dog do when a stranger comes to the door?" to allow owners to objectively characterize 14 aspects of their pet's personalities, including

trainability, attachment, and aggression. Since the survey was developed in 2003, more than 50,000 owners have participated.

The team matched up these behavioral data for each breed with genetic data about breeds from different sets of dogs. They didn't look at genetic and behavioral data for individual dogs, but rather averages across a specific breed. In all, the team identified 131 places in a dog's DNA that may help shape 14 key personality traits. Together, these DNA regions explain about 15% of a dog breed's personality, with each exerting only a small effect. Trainability, chasing, and a tendency to be aggressive toward strangers were the most highly heritable traits, the scientists report in a paper posted this month on the preprint server bioRxiv.

The locations of these DNA hot spots make sense: Some are within or close to genes tied to aggression in humans, for example, whereas DNA associated with the dog's level of trainability is found in genes that in humans are associated with intelligence and information processing.

The findings suggest behavior is guided by the same genes in many species, MacLean says. And if, for example, genes underlying anxiety in dogs lead to those same genes in people, that discovery may ultimately lead to better treatments for anxiety-related disorders, Serpell says. "These are the kinds of things we can see in the future."

Because the genetic and behavioral data come from different sets of dogs, the work cannot link a breed's specific behavioral tendencies to any one gene. "This paper doesn't call out any particular breed for its behavior. It relies on behaviors that are found in many breeds," says Heidi Parker, a genome scientist at the National Human Genome Research Institute who, with Ostrander, pioneered some of the early work on dog genomes.

Thus, for example, Serpell's behavioral work has shown that pit bulls are aggressive toward other dogs but not people, but this new analysis can't lead to a DNA test of that behavior. However, Serpell and his colleagues are starting more studies looking at the DNA linked to within-breed variation in behavior, a step in that direction. Such work has been done on a small scale to pinpoint the gene for superfriendly behavior.

Until more of those connections are made, "I am not sure how widely accepted the results will be," says Robert Wayne, an evolutionary biologist at the University of California, Los Angeles. He and dog genetics expert Elinor Karlsson from the University of Massachusetts Medical School in Worcester point out that this study finds a much bigger role for genetics in shaping behavior than previous studies and so think more work needs to be done to verify the findings.

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Mile-High Tsunami That Spread Through Earth's Oceans

Tsunami caused chaos throughout the world's oceans

By Laura Geggel, Senior Writer

When the dinosaur-killing asteroid collided with Earth more than 65 million years ago, it did not go gently into that good night. Rather, it blasted a nearly mile-high tsunami through the Gulf of Mexico that caused chaos throughout the world's oceans, new research finds.

The 9-mile-across (14 kilometers) space rock, known as the Chicxulub asteroid, caused so much destruction, it's no wonder the asteroid ended the dinosaur age, leading to the so-called Cretaceous-Paleogene (K-Pg) extinction.

"The Chicxulub asteroid resulted in a huge global tsunami, the likes of which have not been seen in modern history," said lead researcher Molly Range, who did the research while getting her master's degree in the Department of Earth and Environmental Sciences at the University of Michigan.

Range and her colleagues presented the research, which has yet to be published in a peer-reviewed journal, at the American Geophysical

Union's annual meeting on Dec. 14 in Washington, D.C. And the research, first reported by EOS, is novel. "As far as we know, we are the first to globally model the tsunami from impact to the end of wave propagation," Range told Live Science.

The idea for the project got started when Range's two advisors — Ted Moore and Brian Arbic, both in the Department of Earth and Environmental Sciences at the University of Michigan — realized there was a glaring gap in the Chicxulub research field. Mainly, no one had published a global simulation of the tsunami the asteroid created.

"It wasn't until starting this project that I realized the actual scale of this tsunami, and it's been a fun research story to share," Range said.

Getting to work

The researchers knew that the asteroid hit shallow water in the Gulf of Mexico. But to correctly model its huge impact, they needed a model that could compute "the large scale deformation of the [Earth's] crust that formed the crater, as well as the chaotic waves from the initial blast of water away from the impact site, and waves from ejecta falling back into the water," Range said. So, the group turned to Brandon Johnson, an assistant professor who studies impact cratering at Brown University in Rhode Island.

Johnson ran a model detailing what happened in the 10 minutes following the impact, when the crater was nearly a mile deep (1.5 kilometers) and the blast was so powerful, there wasn't any water in the crater yet. "At this point, some water was moving back toward the crater," Range said. According to the model, "this water will then rush into the crater and then back out, forming the 'collapse wave.'"

In a second model, the team studied how the tsunami propagated through oceans around the world. They did this by taking the results from the first model (particularly the crater shape) and the impact's waves with respect to resting sea level and water speeds, Range said. They then used data sets on the ancient terrain of the ocean, and used that to determine how the tsunami would have played out.

The results show the effects of the tsunami were felt all around the world.

"We found that this tsunami moved throughout the entire ocean, in every ocean basin," Range said. In the Gulf of Mexico, water moved as fast as 89 mph (143 km/h), she found. Within the first 24 hours, the effects of the tsunami's impact spread out of the Gulf of Mexico and into the Atlantic, as well as through the Central American seaway (which doesn't exist anymore, but used to connect the Gulf to the Pacific).

After the initial nearly mile-high (1.5 km) wave, other huge waves rocked the world's oceans. In the South Pacific and North Atlantic, waves reached a whopping maximum height of 46 feet (14 m). In the North Pacific, they reached 13 feet (4 m). Meanwhile, the Gulf of Mexico saw waves as high as 65 feet (20 meters) in some spots and 328 feet (100 m) in others.

To put that in perspective, the largest modern wave ever recorded in the Southern Hemisphere was a "measly" 78 feet (23.8 m) tall, which struck near New Zealand in May 2018, Live Science previously reported.

Hard evidence

There's evidence that supports the models, Range said. According to the second model, fast-moving water from the impact likely caused erosion and sediment disruption in South Pacific, North Atlantic and Mediterranean ocean basins.

In a separate study (which also has yet to be published), Moore examined sediment records across the ocean. His findings agree with the tsunami model, Range said.

It can be hard to imagine such a cataclysmic tsunami, so the researchers compared it to the 2004 Indian Ocean tsunami that killed at least 225,000 people. The two tsunamis were as different as night

and day, they found. "Over the first 7 hours of both tsunamis, the [Chicxulub] impact tsunami was 2,500 to 29,000 times greater in energy than the 2004 Indian Ocean tsunami," Range said.

Of course, the giant tsunami wasn't the only event that did in the non-avian dinosaurs. The asteroid also triggered shock waves and sent a vast amount of hot rock and dust into the atmosphere, which rubbed together with so much friction that they started forest fires and cooked animals alive. These particles also hovered in the atmosphere and blocked the sun's rays for years, killing plants and the animals that ate them.

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"Scary" reality: Meds tainted with germs, glass, carcinogens, mystery particles

"Our drug quality is probably not what we think it is."

Beth Mole - 1/8/2019, 5:40 AM

An investigation by Kaiser Health News into thousands of recent drug recalls reveals a frightening record of medicines in the US being tainted with dangerous bacteria, mold, glass shards, rubber bits, cancer-causing chemicals, mysterious powders, and worrying metal particles. There were also cases of medications with too much or too little ingredients—or simply the wrong ingredients entirely.

Digging deeper, the investigation discovered that a startling number of the drug makers who issued the recalls had received an all-clear from Food and Drug Administration inspectors within a year of their recalls. FDA records and lawsuits suggest that drug makers can easily game the inspection system, mislead inspectors, lie about where drugs are manufactured, or outright sabotage inspections.

For instance, FDA enforcement documents reveal that employees at one drug-making facility in Japan stood "shoulder-to-shoulder" to physically block an FDA inspector from looking around, and another drug maker in India faked a worker strike and cut the lights at its facility to foil an inspection. In a different case, whistleblowers alleged in a lawsuit that Gilead Sciences told the FDA that it used a facility in South Korea to make an ingredient for HIV drugs Truvada and Atripla, but in reality, Gilead was using an unregistered facility in China. The civil suit claimed that the Chinese ingredient contained "glass-like shards," "black rubber-like particles," "plastic-like particles," "small stone or pebble-like particles" and "metal shards."

In facilities where the FDA does find problems, the agency can send warning letters, but it does not issue fines and lacks the authority to issue mandatory drug recalls.

Though only a fraction of the drugs in the country are recalled and bad-apple manufacturers may be the minority, experts express concern about the overall quality control in the US. "Our drug quality is probably not what we think it is," Erin Fox told KHN (Fox purchases medicines for University of Utah Health hospitals). The reality, she added, is "scary."

For its investigation, Kaiser Health reviewed lawsuits, FDA documents, and details of 8,000 drugs recalled since 2013. More than half of those recalls were for drugs made in facilities with FDA citations. But nearly 700 recalls were for drugs made in facilities that had recently passed inspections. The remainder of the recalls were for drugs from facilities that hadn't been inspected in at least five years.

Recalling recalls

KHN's investigation comes on the heels of highly publicized recalls of widely used blood pressure medications. The medications were recalled after the discovery that they were contaminated with cancer-causing chemicals.

Those drugs were made in overseas facilities, which are often feared for being the source of safety and quality issues. But domestic facilities have also been the source of problems. As an example, the KHN investigation highlighted the case of a Florida facility that produced stool softener later recalled over contamination

with *Burkholderia cepacia* bacteria. The Centers for Disease Control and Prevention linked more than 100 confirmed and suspected infections in 12 states to the drug.

KHN reporters told the story of one of those cases, a six-month-old baby boy in Michigan. He was in the hospital awaiting a heart transplant in 2016 when medical providers gave him the stool softener. He went on to develop a severe respiratory infection with *B. cepacia*, which landed him in intensive care. His status on the transplant list was put on hold, and his heart condition worsened. He has been on a ventilator ever since. Sharp hospital staff traced his infection—and others—back to the stool softener.

The baby's family is now suing the drug maker, PharmaTech, which didn't respond to a request for comment but has denied the lawsuit's claims in court documents. That's despite the FDA investigation in the late summer of 2016 that determined *B. cepacia* was in the water PharmaTech used to clean its equipment. The FDA concluded that its drugs had been contaminated for a year, and the company issued its recall in August of 2016. PharmaTech's facility, however, had passed a previous FDA inspection in March of 2016.

An FDA spokesperson told KHN that, "While the FDA would prefer that no drug be distributed that later is recalled, we do not think that a recall indicates a failure of FDA inspection and surveillance programs."

https://wb.md/2H9pJot

'Distressing' Trend: Cervical Cancer Increasing in Japan

In contrast with the trend seen in most other developed countries, cervical cancer is on the rise among young women in Japan.

Megan Brooks

Cervical cancer is on the rise among young women in Japan. This contrasts with the trend seen in most other developed countries, where rates have been falling, largely as a result of screening and vaccination against human papillomavirus (HPV) — the chief cause of virtually all cervical cancers worldwide.

The recent increase in cervical cancer in Japan can probably be explained by several factors, say researchers: low levels of cervical cancer screening, changes in sexual behavior leading to an increase in the prevalence of HPV infection, and the suspension in June 2013 of an active recommendation of HPV vaccination.

"The most important finding in the paper is increasing incidence of cervical cancer among recent birth cohort in Japan, suggesting an increasing prevalence of HPV," Mai Utada, PhD, of the Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan, told *Medscape Medical News*.

"Screening and vaccination have been shown to be highly effective and, if duly strengthened, would help reverse the distressing cervical cancer trends in Japan," Utada and colleagues write.

The study was published online November 25 in the *International Journal of Cancer*.

An "Urgent Concern"

Using registry data, the researchers analyzed trends in the incidence of cervical cancer in Japan from 1985 to 2012, relative to trends among Japanese Americans in Surveillance, Epidemiology, and End Results (SEER) registries and among women in South Korea in the Korea Central Registry.

According to the Japanese registry data, 6760 invasive cervical cancer cases were diagnosed in women aged 20 to 84 between 1985 and 2012. Incidence rates in Japan have been rising since the late 1990s, driven largely by a cohort effect of increasing risk in birth cohorts after 1960, the researchers say.

Between 1997 and 2012, the age-standardized incidence rate increased significantly by 2.6% per year, after a significant decline of 1.7% per year between 1985 and 1997, they report.

Trends in age-specific incidence rates varied. Among women younger than 50 years, there was a steady, significant increase in incidence rates between 1985 and 2012. The highest annual percentage change per year occurred in the youngest women (5.1% for women aged 20 to 29, 3.2% for those aged 30 to 39, and 1.7% for women aged 40 to 49). Incidence rates were stable among women aged 50 to 54. For those aged 55 years and older, incidence rates decreased significantly in the 1980s and 1990s.

Notably, say the researches, the increasing cervical cancer risk seen among recent birth cohorts in women in Japan was not observed in Japanese American or South Korean women. In contrast, the incidence rate was declining among Japanese American women of all ages and in all but the youngest (<30 years) South Korean women.

The increasing risk for cervical cancer among young women in Japan is "an urgent concern," Utada and colleagues say. It is likely related to "increasing HPV infection prevalence unopposed by comprehensive screening and, going forward, HPV vaccination," they write.

Cervical cancer screening was initiated in Japan in 1983, but there is no systematic call-and-recall system, and there is wide variation in screening. Nationally, screening uptake remains low, the researchers note. Screening uptake in the United States and South Korea is significantly higher than in Japan.

As for vaccination, the Japanese Ministry of Health, Labour, and Welfare's 2013 recommendation to suspend HPV vaccine led to a drastic decline in vaccination rate, the authors note. As previously reported by *Medscape Medical News*, the rate of newly vaccinated girls in fiscal year 2013 dropped from the usual rate of approximately 70% per year to 1.1% in 12-year-old girls and to 3.9% in 13-year-old girls.

HPV prevalence is tied to the age at which sexual activity starts. In Japan, because of shifts in attitudes toward sexuality among teenagers, girls are having sex at younger ages, the researchers note. It is likely that similar changes occurred in the United States and South Korea, but in those countries, rates of screening may have increased, they say.

In March 2017, the American Society of Clinical Oncology issued a global guideline offering evidence-based recommendations on the use of HPV vaccination for the prevention of cervical cancer. The guideline took into account the varying levels of economic and structural resources, depending on the circumstances of each country. Last May, the World Health Organization called for all countries to take action to help end the suffering caused by cervical cancer.

The study was supported by grants from the Radiation Effects Research Foundation, Japanese Ministry of Health, Labour and Welfare, and the US Department of Energy. The authors have disclosed no relevant financial relationships.

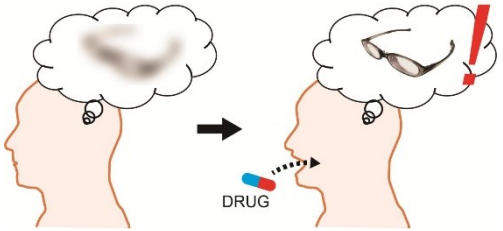
Int J Cancer. Published online November 25, 2018. Abstract

http://bit.ly/2SRGNRx

Do you recognize this image?

Drug can boost long-term memory of objects

Allergy sufferers may use antihistamines to reduce symptoms, but new research reveals that better long-term memory might be possible with pro-histamine treatment. Long-term memory is used to remember anything before 48 hours ago.



Researchers at the University of Tokyo led by Professor Yuji Ikegaya studied the effect of histamine on long-term memory. After taking a drug to boost levels of histamine in the brain, adults in their mid-20s had improved long-term memory test scores and mice temporarily had memories that lasted 25 days longer than normal. **Image by Yuji Ikegaya and Hiroshi Nomura CC-BY**

During recent studies by researchers in Japan, histamine improved people's long-term memory test scores depending on the strength of

the original memory and could temporarily extend mice memories by as much as 25 days longer than normal.

Clarifying the role of histamine in memory may help alleviate symptoms of memory disorders, such as Alzheimer's disease and other forms of dementia.

Professor Yuji Ikegaya and lecturer Hiroshi Nomura, Ph.D., of the University of Tokyo led a research team that included collaborators at Hokkaido University and Kyoto University in Japan.

Recognize this?

A total of 38 men and women in their mid-20s completed memory tests on three different days. Participants looked at pictures of familiar objects, like eyeglasses or a wristwatch, and then several days later were shown some of the same images, as well as some similar and some new photos, and were asked if they had seen the image before.

"In real life, we cannot know what we forgot. This is why we do human memory tests with pictures on a computer screen," said Ikegaya.

Seven or nine days later, participants were given either a placebo (a "sugar pill," or fake medicine) or a large dose of a medication that increases the amount of histamine in the brain. The unusually large dose ensured the medication crossed the blood-brain barrier, the body's natural defense that makes it difficult for medication to reach the brain. The same medication is normally prescribed at lower doses to treat dizziness.

Duality

After taking the drug, participants with poor memories recognized more images correctly, while images that had been difficult to recall became easier for all participants to recognize. However, taking the drug lowered scores of participants with good memories, and images that had been easier to recall became slightly more difficult for all participants to recollect.

"To any students thinking about using this drug as a study aid, I must warn them to first always protect their health, and second to realize that we have not tested whether this drug helps anyone learn or memorize new things," said Ikegaya.

"Increased histamine helped research participants remember an image they knew once but couldn't remember during a long-term memory word-association test," said Ikegaya.

Researchers suspect that the phenomenon of stochastic resonance, adding white noise to a transmission to boost signal strength, may cause the dual effect of histamine improving long-term memory sometimes but hindering it at other times.

Histamine threshold

Ikegaya suggests memory is a combination of a gradient system and a yes:no or 1:0 digital system. Information might be stored in the brain as a gradient, but nerves do not fire until they are above a particular threshold. Below this threshold is "no" or 0, and we cannot remember. Above this threshold is "yes" or 1, and we can remember.

"You still have the memory, but you can't access it unless it is above a particular threshold," said Ikegaya.

Researchers suspect that the drug raises the histamine gradient to the point that the neurons involved in the latent memory reach the threshold level required to fire a signal and make us remember. However, for memories already over the threshold naturally, extra histamine adds too much noise and excessive nerve signaling hinders recall. Histamine had no effect on participants' scores on tests unrelated to long-term memory.

Mice memories

Researchers gave mice two plastic toys, one the mice were given before and another that was new. Mice prefer to explore a new toy, but after three days, mice forget and treat all toys as new. After receiving a medication that increases histamine in the brain, mice could recognize toys they'd seen as long as 28 days ago.

The long-term memory boost was temporary, though. On day 29, all toys were new again to the mice. Researchers saw similar results with two different drugs that increase histamine: thioperamide and betahistine.

Experiments to examine the activity of individual neurons in mouse brains revealed that the drugs increased histamine specifically in a brain region known to be involved in visual perception and memory, called the perirhinal cortex. Moreover, histamine reactivated the same neurons that were active in making the memory.

Bad memories

Improved long-term memory is not always beneficial, such as for sad or fearful memories, or in disorders such as post-traumatic stress disorder (PTSD).

Remembering and forgetting are not simple opposites. Instead, researchers suspect that different brain regions and processes are involved in remembering and forgetting. "If we have typical memory, then there is a balance between the brain systems for remembering and for forgetting. Too much forgetting or too much remembering is likely an upset of that balance," said Ikegaya.

Future memories

Researchers are currently planning future studies to test how histamine levels might affect memory test results in older adults. Other studies will also examine how histamine might be involved in prospective memory, the "don't forget" type of memories for the future, such as things we might write on reminder sticky notes to our future selves.

About the research

This research published in the journal *Biological Psychiatry* is peer-reviewed and included experimental studies in mice and small-scale randomized control trials in people.

The neurotransmitter histamine affects the immune response, memory and acid levels in the stomach. Specialized receptors in different areas of the body regulate the different functions of histamine.

Professor Ikegaya has written multiple popular nonfiction science books in Japanese, including Shinkashisugita Nou (The Over-Evolved Brain, ISBN: 978-4062575386) and Kaiba: Nou wa Tsukarenai (Hippocampus: The Untiring Brain, ISBN: 978-4255001548).

Journal Article

Hiroshi Nomura, Hiroto Mizuta, Hiroaki Norimoto, Fumitaka Masuda, Yuki Miura, Ayame Kubo, Hiroto Kojima, Aoi Ashizuka, Noriko Matsukawa, Zohal Baraki, Natsuko Hitora-Imamura, Daisuke Nakayama, Tomoe Ishikawa, Mami Okada, Ken Orita, Ryoki Saito, Naoki Yamauchi, Yamato Sano, Hiroyuki Kusuhara, Masabumi Minami, Hidehiko Takahashi, Yuji Ikegaya. Central histamine boosts perirhinal cortex activity and restores forgotten object memories. 8 January 2019. Biological Psychiatry. *DOI: 10.1016/j.biopsych.2018.11.009*

http://bit.ly/2FrPyOh

How common pain relievers may promote Clostridium difficile infections

Observational studies have identified a link between severe C. difficile infections and use of NSAIDs

Washington, DC - *Clostridium difficile* causes the most common and most dangerous hospital-born infections in the United States and around the world. People treated with antibiotics are at heightened risk because those drugs disturb the microbial balance of the gut, but observational studies have also identified a link between severe *C. difficile* infections and use of NSAIDs, or non-steroidal anti-inflammatory drugs. The study is published in the journal, *mBio*.

Findings published this week provide new evidence for that connection, as well as an explanation of the underlying biological mechanism. A better understanding of how NSAIDs affect the severity of *C. difficile* infection could inform the development of future treatments.

"We are always trying to think of modifiable risk factors for the disease," says study leader David Aronoff, a microbiologist and

infectious diseases expert at Vanderbilt University in Nashville, Tennessee. Aronoff worked on the study with researchers from the University of Michigan and the University of Arizona.

The researchers followed two groups of antibiotic-treated mice for one week after infection with *C. difficile*. One group had been treated with an NSAID called indomethacin prior to infection, and the other hadn't. Only about 20 percent of the mice treated with the NSAID survived to the end of the observation period, compared to about 80 percent of the mice that hadn't been exposed to the NSAID.

Aronoff and his collaborators determined that even brief exposure to the NSAID prior to *C. difficile* inoculation increased the severity of infections and shortened survival. Further cellular and genetic analyses revealed that the NSAID exposure altered the gut microbiota and depleted the production of prostaglandins, hormone-like substances known to play an important role in gastrointestinal health.

Those observations align with previous studies reporting that NSAIDs can cause or exacerbate an inflammatory disease called colitis, also by inhibiting the body's production of prostaglandins.

In the new study, the researchers conclude that NSAID-driven changes worsened *C. difficile* infections by impairing epithelial cells - the main defense system in the intestine against infectious taxa - and by disturbing the normal immune response. They studied at the impact of only one NSAID, indomethacin, but Aronoff says he thinks the findings might extend to other common NSAIDs, including ibuprofen and aspirin, since they all have roughly the same biological mechanism.

"Ultimately, these new results might guide how we treat people with C. diff, particularly with pain management," says Aronoff. "Right now, it's too early for our results to guide clinical care, but they should be a stimulus for future studies."

http://bit.ly/2VRXdLl

No evidence to support a formal health claim for cocoa, researchers find

A review of recent studies into flavanols and blood pressure reveals inconsistent outcomes.

Andrew Masterson reports.

The evidence that chocolate and other cocoa-containing products reduce high blood pressure is not strong enough to warrant an official health claim, a team of Canadian researchers has found.

In recent years several studies have concluded that compounds found in cocoa, called flavanols, work to lower blood pressure.

This has led to many popular online and print publications claiming that chocolate and similar products can be regarded as valuable therapeutics.

Typical is the website medicinehunter.com, which calls cocoa "a titan of health benefits", stating that "even small amounts of cocoa can reduce cholesterol in the blood, and can lower blood pressure".

Under current guidelines, about 50% of the population of the US is classified as having hypertension, so, clearly, any move to recognise cocoa and chocolate as a beneficial treatment represents a staggeringly large business opportunity.

Research has shown that flavanols – phytochemicals comprising epicatechin, catechin and procyandins – can reduce blood pressure by increasing levels of nitric oxide.

However, critical issues such as dosage and long-term effects remain uncertain, matters complicated by wildly divergent experimental protocols and, in some cases, the involvement of vested interests in funding research.

In 2017 the research organisation Cochrane conducted a meta-analysis of 40 pilot treatments and found that overall they revealed "a small but statistically significant lowering of blood pressure".

However, the researchers added that the evidence was only of "moderate quality", and was entirely absent in some crucial aspects.

"We were unable to identify any randomised controlled trials that tested the effect of long-term daily use of cocoa products on blood pressure, and there were no trials that measured the health consequences of high blood pressure, such as heart attacks or strokes," they wrote.

Now, writing in the journal *Trends in Food Science and Technology*, Canadian scientists led by Yidi Wang from the University of Manitoba, conclude the evidence is substantially weaker than previously thought.

Wang and colleagues reviewed 17 studies from the past 20 years that investigated the relationship between cocoa flavanols and blood pressure.

Only nine of the papers reported that blood pressure was lowered. "This indicated the evidence of cocoa flavanols on BP reduction was conflicting," they write.

The researchers thus concluded that the data upon which any formal health claim must rest is "inconsistent", and noted the "lack of high quality studies" in the field.

There is, they note, no evidence to push for regulatory bodies to pass an "authorised health claim" for cocoa or chocolate.

For the moment, thus, the best cocoa marketers and natural health gurus can legally get away with in the US is a kind of vague and fluffy suggestion that cocoa and chocolate, while undoubtedly tasting very nice indeed, might make you feel a bit better, maybe, perhaps.

"Considering the health claim systems in the US, a qualified health claim with the category 'C' can be attributed to cocoa flavanol intake and BP reduction, reflecting a low level of scientific evidence supporting the claim," Wang and colleagues state.

https://wb.md/2AJ05S1

A Decidedly Darker Prognosis for Takotsubo Syndrome

Takotsubo syndrome (TS) has been considered a transient benign disorder, but mounting evidence of a darker long-term prognosis is reshaping that belief.

Patrice Wendling

A systematic review of 54 studies involving 4679 patients showed relatively high rates of life-threatening complications such as acute heart failure (HF) with shock (19%) and malignant arrhythmias (10%), with in-hospital death occurring in 1.8% of cases.

Among survivors, 1% had a recurrent episode of TS and 3.5% died per year over a median follow-up of 28 months (range, 6-99 months).

"We now know that Takotsubo syndrome is not a benign disease and is associated with important in-hospital and, more importantly, long-term mortality rates," study author Francesco Pelliccia, MD, PhD, Department of Cardiovascular Sciences, La Sapienza University, Rome, told *theheart.org | Medscape Cardiology*.

Although the review included only original studies and excluded multicenter international registries to avoid overlap between cohorts, the results are comparable with registry findings, he said.

"The advantage is that it really represents a real-world experience much more than other international registries, which have data only from Takotsubo syndrome centers," Pelliccia said.

The study was published January 3 in the *Journal of the American College of Cardiology: Heart Failure.*

"Basically it confirms what we published three years ago," said Thomas Lüscher, MD, FRCP, from the Royal Brompton & Harefield Hospital Trust and Imperial College, London, and the University of Zurich, Switzerland.

They published in-hospital and long-term mortality rates of 4.1% and 5.6%, respectively, among 1750 patients in the International

Takotsubo Registry (InterTAK), a consortium of 26 centers in Europe and the US.

Last year, similarly high short- and long-term mortality rates were reported in 711 patients in Spain's National Registry on Takotsubo Syndrome (RETAKO) (2.4% and 4.6%/yr) and in a study of 826 TS patients with and without diabetes in the German Italian Stress Cardiomyopathy (GEIST) registry (6.4% vs 5.7%; 31.4% vs 16.5%).

"It's quite clear that the mortality currently and acute cardiogenic shock rate is the same as in patients with infarction treated according to current possibilities, so I think it has to be taken seriously," said Lüscher, who is among those proposing TS as a microvascular acute coronary syndrome.

Nevertheless, change comes slowly, he said. Takotsubo syndrome, often called broken heart syndrome or stress cardiomyopathy, continues to be underdiagnosed and the risk for adverse events underappreciated.

"Most physicians still believe it is a benign condition," Lüscher said. "I just did a case this morning in an elderly, postmenopausal lady who came in with pulmonary edema who couldn't lie flat, had water on the lungs, and had blood pressure that was low, and they didn't even dare to do an angiogram and today we proved she had Takotsubo."

Along with current uncertainty about the natural history of TS, Pelliccia and colleagues note that it remains unclear whether presenting characteristics in the acute phase are associated with long-term prognosis.

Of the 4679 patients analyzed, the average ages ranged from 53 to 75 years and 87% were women. TS was preceded in two thirds of patients by an emotional (36%) or physical (36%) stressor.

Two thirds of patients presented with chest pain (64%) and roughly half had signs of acute heart failure (26% dyspnea, 19% shock). Moderate functional left ventricular (LV) dysfunction was present in most patients, with a mean LV ejection fraction ranging from 28% to 54% (mean, 40%). The typical pattern of TS characterized by apical ballooning was found in 72%.

Cardiovascular risk factors including hypertension (59%) and diabetes (34%) were common, while a few studies also reported concurrent neurologic (15%) and psychological diseases (18%) and cancer (17%).

Most of the deaths (78%) were due to noncardiac causes, suggesting that concomitant conditions play a major, long-term prognostic role, the authors note.

Meta-regression analysis showed that long-term mortality was significantly associated with older age (P = .05; coefficient, 0.002), physical stressor (P = .0001; coefficient, 0.001), and an atypical ballooning pattern (P = .009; coefficient, 0.001). HF at presentation, however, was not a significant determinant of TS recurrence or long-term mortality.

"We now have indicators that might constitute red flags to us that signal there might be an increased risk after an acute episode," Pelliccia said. "We have to pay particular attention to whether or not our patients are vulnerable, as defined by their relative function, age, presence of comorbidities, and evidence of more extensive damage at time of the acute phase."

Limitations of the study include the lack of control groups and the inability to investigate the cause of death or assess the effects of medication on long-term outcomes, he said. Although most patients were discharged on an angiotensin-converting enzyme inhibitor (ACE)/angiotensin receptor blocker (ARB) (92%) or beta-blocker (54%), there was "extreme heterogeneity" in medications during follow-up.

"We noticed that patients were treated differently in different countries, in different centers," Pelliccia said. "There were those who received beta blockers but not ACE inhibitors during follow-up and

we now have preliminary data showing that ACE inhibitors are effective in this, whereas beta blockers are not."

"There's no really good treatment yet," said Lüscher, who coauthored a new expert international consensus document on Takotsubo, published in 2018. "In fact, if you give catecholamines, this may actually be detrimental in these patients because they contract at the base of the heart, and if you stimulate at only the base of the heart you get a gradient across the left ventricular outflow tract, and blood pressure may actually go down rather than up. So it is a tricky thing."

He noted that a large trial is being planned in the United Kingdom, but would not reveal details other than to say efforts need to focus on interfering with microvascular and endothelial dysfunction, which continue to exist in TS outside the acute event.

In the acute setting, research is needed to assess devices like extracorporeal membrane oxygenation (ECMO) that unload the heart until it recovers in severe cases that develop hypotension.

"I haven't used the *Impella* but conceptually it's a good device because it takes the blood from the apical ballooning up the aorta," he said. "We've done quite a few cases with ECMO, which is quite invasive, but saved quite a few patients with this intervention. But this is all evidence-based; this has not been tested in a trial."

In a related editorial, L. Christian Napp, MD, Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany, writes: "We can conclude that TS carries considerable risk, especially if a physical trigger is present, and it is not a 'self-healing syndrome.' "

However, some "big black holes" remain that still make it difficult to treat and consult patients with TS, he notes, including the true pathogenesis of TS; how patients should be treated during the acute phase, especially when shock develops; whether patients need long-term medical therapy; and the allegedly transient nature of TS.

"To answer the open questions, we should aim for prospective studies with comprehensive data acquisition in the acute phase and systematic follow-up including the cause of death," Napp concludes. "Given the existing recurrence rate and the still huge amount of beta-blockers prescribed without data, studies aiming to test medical therapies are needed."

Senior author Paolo G. Camici has been a consultant for Servier; all other authors have disclosed no relevant financial relationships. Lüscher has disclosed no relevant financial relationships. Napp reported receiving modest, personal fees for lectures, proctorship, consulting, or travel support from Abiomed, Maquet, Cytosorbents, Bayer, Zoll, Amgen, Biotronik, Merit Medical, Servier, and Terumo.

J Am Coll Cardiol HF. Published online January 3, 2019. Abstract, Editorial

http://bit.ly/2VNwiR0

Stem cells used to trace autism back to the formation of neurons

Gene-activity changes come before any visible differences in neurons.

John Timmer

While autism is a spectrum of disorders, it's clear that the more significant cases involve physical differences in the brain's nerve cells. Several studies have reported an excess in connections among neurons in the brains of people with autism. But when does this happen? Changes in neural connections are key components of learning and memory, and they can happen at any point in life; major reorganizations in connectivity occur from before birth up to the late teens.

Anecdotal reports of autism's symptoms often suggest an onset between one and two years old. But a new study places the critical point extremely early in embryo development—at a point before there are any mature nerve cells whatsoever.

A series of challenges

Figuring out how autism starts is complicated. To begin with, it's a spectrum that might include more than one disorder. You also can't

know in advance who's going to develop it, so you can only look at it retrospectively, after the problems are apparent. Finally, the human brain is simply not something you can ethically do invasive experiments on.

The new work relies on techniques that weren't available just a few decades ago. We now know how to take skin cells and convert them to stem cells. We're able to direct stem cells to develop along the lineages that contribute to brain development. And we can structure that development in three dimensions to produce a miniature version of the mature tissue, termed an organoid. Combined, these approaches allow us to study the development of autism using nothing more than a small skin sample from autistic individuals.

For the new research, a large international team obtained skin cells from eight autistic people and five controls. These were converted into stem cells and then induced to develop along a pathway that leads to brain-like neurons. This pathway includes an intermediate step, called a neural stem cell, in which the cells are committed to developing as nerve cells but haven't adopted a mature, specialized nerve cell identity (mature cells belong to distinct populations, like serotonin-producing dentate gyrus cells, etc.). As had been seen in past studies, the mature nerve cells derived from autistic individuals created very complex patterns of branching axons compared to control cells.

At five different time points during the development of these cells, the researchers separated out the nerve cells or nerve-cells-to-be. Then they obtained all the RNA from the cells, which provides a window into gene activity. Next, the researchers performed a computational analysis to identify groups of genes that were active at specific steps. This identified three distinct groups of genes (which they termed "modules") that defined distinct stages of the developmental process. You can think of these stages as pre-neuron, neural stem cell, and maturing neuron.

Accelerated development

When these modules were compared in cells from autistic individuals and controls, there weren't many differences in the two that marked later stages of development. The earliest active module, however, appeared to be active on an accelerated schedule in the cells that came from autistic individuals. In other words, while normal cells might reach a given stage of gene activity at day four, those from autistic patients might reach that at day two. This accelerated pace was also apparent in the physical changes the cells undergo as they mature.

The earliest two modules also contain a number of genes that had previously been identified as enhancing the risk of autism. And expression of some of these genes at early stages in the process could mimic the progression of autism, accelerating the developmental process.

The timing of all of this suggested to the authors that the problems in these autistic individuals came from the process of forming neural stem cells. This sets the stage for problems in everything that comes after it.

To test this idea, the authors came up with a clever solution. People have identified a way to bypass the neural stem cell stage of the process and force stem cells to develop directly into neurons. (Surprisingly, all this takes is the expression of a single gene.) If the specification of neural stem cells is where things go wrong, then skipping it entirely might rescue the problems. And, in fact, it does. The complexity of neural branching was similar in the experimental and control cells when neurons were generated using this approach.

We haven’t “solved” autism

It's important to emphasize that this research doesn't mean we've "solved" autism in any way. The participants in this study were selected as having a single symptom that clearly placed them on the autism spectrum; it's not clear whether these results will apply to

those who are on the spectrum due to other symptoms. And there's a big difference between knowing something goes wrong during neural stem cell generation and knowing what, exactly, has gone wrong. So there's still a lot of work to do here.

But the results do indicate that, at least in some individuals with autism, problems start extremely early. In humans, neural stem cells are specified before three weeks into the pregnancy—a point when many people aren't even aware or certain they're pregnant. Depending on how general this is, that may mean that interventions at the earliest stages of autism—either by directly addressing the problem or by limiting any environmental influences that promote autism—is pretty unlikely.

While this is an impressive body of work on its own, what's really striking is how it puts together so many techniques that are relatively recent developments. These include the use of stem cells to study diseases that are otherwise difficult to address experimentally, the ability to do large-scale RNA sequencing, and the algorithms that let us analyze this data—all are relatively recent developments. Biology is filled with incremental developments, and it's only when you stop to consider what had to happen before research like this was even possible that the rate of progress can be appreciated.

Nature Neuroscience, *2019. DOI: 10.1038/s41593-018-0295-x (About DOIs).*

https://go.nature.com/2FnMzak

Earth's magnetic field is acting up and geologists don't know why

Erratic motion of north magnetic pole forces experts to update model that aids global navigation.

Alexandra Witze

Something strange is going on at the top of the world. Earth's north magnetic pole has been skittering away from Canada and towards Siberia, driven by liquid iron sloshing within the planet's core. The magnetic pole is moving so quickly that it has forced the world's geomagnetism experts into a rare move.

On 15 January, they are set to update the World Magnetic Model, which describes the planet's magnetic field and underlies all modern navigation, from the systems that steer ships at sea to Google Maps on smartphones.

The most recent version of the model came out in 2015 and was supposed to last until 2020 — but the magnetic field is changing so rapidly that researchers have to fix the model now. "The error is increasing all the time," says Arnaud Chulliat, a geomagnetist at the University of Colorado Boulder and the National Oceanic and Atmospheric Administration's (NOAA's) National Centers for Environmental Information.

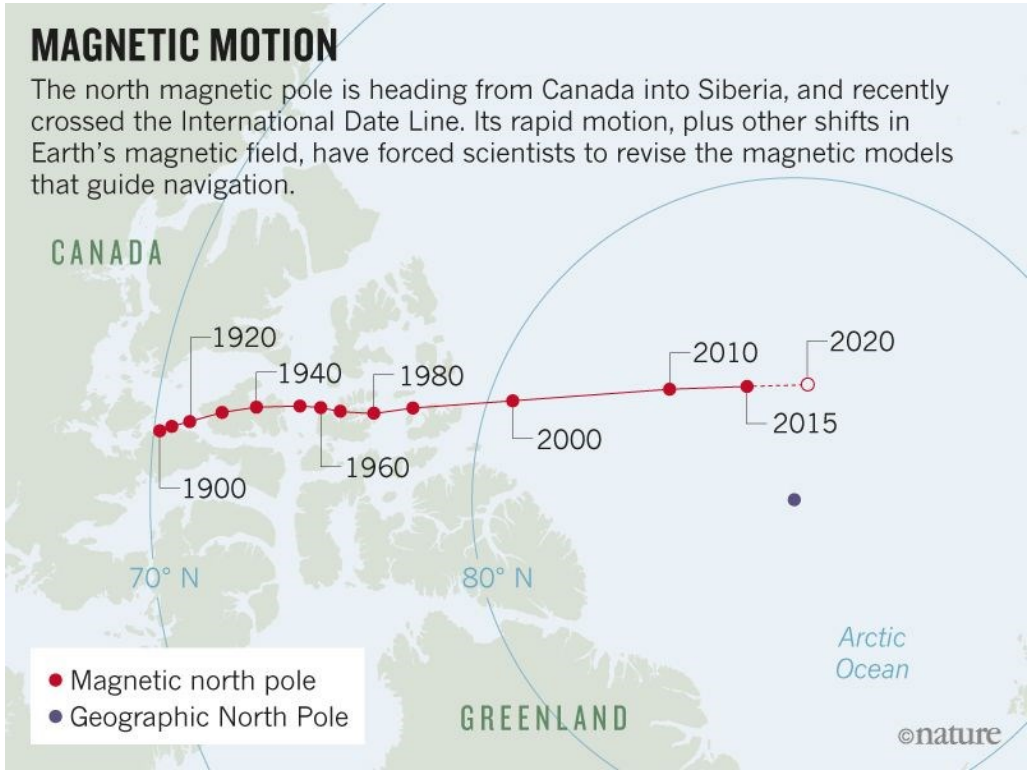
The problem lies partly with the moving pole and partly with other shifts deep within the planet. Liquid churning in Earth's core generates most of the magnetic field, which varies over time as the deep flows change. In 2016, for instance, part of the magnetic field temporarily accelerated deep under northern South America and the eastern Pacific Ocean. Satellites such as the European Space Agency's Swarm mission tracked the shift.

By early 2018, the World Magnetic Model was in trouble. Researchers from NOAA and the British Geological Survey in Edinburgh had been doing their annual check of how well the model was capturing all the variations in Earth's magnetic field. They realized that it was so inaccurate that it was about to exceed the acceptable limit for navigational errors.

Wandering pole

"That was an interesting situation we found ourselves in," says Chulliat. "What's happening?" The answer is twofold, he reported last month at a meeting of the American Geophysical Union in Washington DC.

First, that 2016 geomagnetic pulse beneath South America came at the worst possible time, just after the 2015 update to the World Magnetic Model. This meant that the magnetic field had lurched just after the latest update, in ways that planners had not anticipated.



Source: World Data Center for Geomagnetism/Kyoto Univ.

Second, the motion of the north magnetic pole made the problem worse. The pole wanders in unpredictable ways that have fascinated explorers and scientists since James Clark Ross first measured it in 1831 in the Canadian Arctic. In the mid-1990s it picked up speed, from around 15 kilometres per year to around 55 kilometres per year. By 2001, it had entered the Arctic Ocean — where, in 2007, a team including Chulliat landed an aeroplane on the sea ice in an attempt to locate the pole.

In 2018, the pole crossed the International Date Line into the Eastern Hemisphere. It is currently making a beeline for Siberia.

The geometry of Earth's magnetic field magnifies the model's errors in places where the field is changing quickly, such as the North Pole. "The fact that the pole is going fast makes this region more prone to large errors," says Chulliat.

To fix the World Magnetic Model, he and his colleagues fed it three years of recent data, which included the 2016 geomagnetic pulse. The new version should remain accurate, he says, until the next regularly scheduled update in 2020.

Core questions

In the meantime, scientists are working to understand why the magnetic field is changing so dramatically. Geomagnetic pulses, like the one that happened in 2016, might be traced back to 'hydromagnetic' waves arising from deep in the core[1]. And the fast motion of the north magnetic pole could be linked to a high-speed jet of liquid iron beneath Canada[2].

The jet seems to be smearing out and weakening the magnetic field beneath Canada, Phil Livermore, a geomagnetist at the University of Leeds, UK, said at the American Geophysical Union meeting. And that means that Canada is essentially losing a magnetic tug-of-war with Siberia.

"The location of the north magnetic pole appears to be governed by two large-scale patches of magnetic field, one beneath Canada and one beneath Siberia," Livermore says. "The Siberian patch is winning the competition."

Which means that the world's geomagnetists will have a lot to keep them busy for the foreseeable future.

Update, 9 January: The release of the World Magnetic Model has been postponed to 30 January due to the ongoing US government shutdown.

Nature ***565***, *143-144 (2019) doi: 10.1038/d41586-019-00007-1*

http://bit.ly/2VPHmNp

Two-thirds of stroke survivors are in exceptionally good mental health

Study identifies factors associated with resiliency among stroke survivors

Two-thirds of stroke survivors are in complete mental health despite the impact of their stroke, according to a large, nationally representative Canadian study conducted by researchers at the University of Toronto's Factor-Inwentash Faculty of Social Work.

"It is so heartening to learn that the vast majority of stroke survivors are in optimal mental health, indicating amazing resiliency. Many research studies, including my own earlier publications, have focused on post-stroke depression and suicidal thoughts. This is a paradigm shift to examine stroke survivors who are mentally flourishing" said Professor Esme Fuller-Thomson, lead author of the study and Sandra Rotman Endowed Chair and Director of the Institute for Life Course and Aging at the University of Toronto.

"Our definition of 'complete mental health' sets a very high bar, requiring that respondents were happy and/or satisfied with their life on an almost daily basis and that they were free of suicidal thoughts, substance dependence, depression and anxiety disorder for the past year" stated Fuller-Thomson.

This study shed new light on factors associated with complete mental health among stroke survivors. Having a confidant and being free of chronic pain were important predictors. In contrast, a history of childhood maltreatment and a lifetime history of mental illness decreased one's likelihood of achieving complete mental health after a stroke.

"One of our most exciting findings was the fact that stroke survivors with at least one confidant were four times more likely to be in complete mental health in comparison to those who were socially isolated. This suggests targeted interventions for socially isolated and lonely patients may be particularly helpful in optimizing well-being after a stroke" said co-author Lisa A. Jenson, a recent University of Toronto MSW graduate.

"Not surprisingly, we found that stroke survivors with chronic and disabling pain had much lower odds of complete mental health. Other research indicates that post-stroke pain is often underdiagnosed and undertreated. These findings highlight the importance of health professionals vigilantly assessing and treating stroke survivors for chronic pain" stated Jensen.

"It appears that childhood adversities cast a very long shadow over many, many decades. In this sample of Canadians aged 50 and older, stroke survivors who had a history of childhood physical abuse, sexual abuse or chronic parental domestic violence were only half as likely to be in complete mental health in comparison to those without these childhood traumas." said Fuller-Thomson.

The study was based upon a nationally representative community sample of 11,157 Canadians aged 50 and older, of whom 300 were stroke survivors. Those living in long term care facilities were not included in the survey, so the study does not include some of the most seriously impaired stroke survivors.

The authors emphasize that the findings can only be generalized to older Canadians who are living in the community but not in institutions. The article was published online today in the Journal of Aging and Health.

"We hope that these findings of incredible resiliency in stroke survivors are encouraging to stroke patients, their families and the health profession. There is a light at the end of the tunnel." stated Fuller-Thomson.

Article details: Fuller-Thomson, E & Jensen, L.A. Flourishing After a Stroke: A Nationally Representative Portrait of Resilience and Mental Health Among Older Canadians. Journal of Aging and Health.

http://bit.ly/2D6vE9U

Thousands of stars turning into crystals

The first direct evidence of white dwarf stars solidifying into crystals has been discovered by astronomers at the University of Warwick, and our skies are filled with them

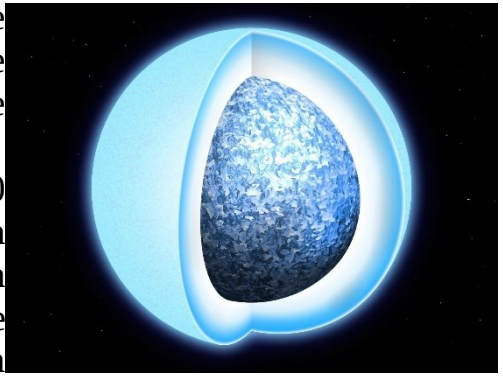
- ***Our own Sun is destined to become a crystal white dwarf in about 10 billion years***
- ***First direct evidence that white dwarf stars form crystal cores of metallic oxygen and carbon***
- ***Crystallisation delays cooling processes, meaning that some stars could be billions of years older than previously thought***
- ***The oldest white dwarfs, nearly the age of the Milky Way, are likely to be almost fully crystal***
- ***Discovery published in* Nature *exactly fifty years after it was predicted***

The first direct evidence of white dwarf stars solidifying into crystals has been discovered by astronomers at the University of Warwick, and our skies are filled with them.

Observations have revealed that dead remnants of stars like our Sun, called white dwarfs, have a core of solid oxygen and carbon due to a phase transition during their lifecycle similar to water turning into ice but at much higher temperatures. This could make them potentially billions of years older than previously thought.

The discovery, led by Dr Pier-Emmanuel Tremblay from the University of Warwick's Department of Physics, has been published in Nature and is largely based on observations taken with the European Space Agency's Gaia satellite.

White dwarf stars are some of the oldest stellar objects in the universe. They are incredibly useful to astronomers as their predictable lifecycle allows them to be used as cosmic clocks to estimate the age of groups of neighboring stars to a high degree of accuracy. They are the remaining cores of red giants after these huge stars have died and shed their outer layers and are constantly cooling as they release their stored up heat over the course of billions of years.



White dwarf star in the process of solidifying. **University of Warwick/Mark Garlick**

The astronomers selected 15,000 white dwarf candidates within around 300 light years of Earth from observations made by the Gaia satellite and analysed data on the stars' luminosities and colours.

They identified a pile-up, an excess in the number of stars at specific colours and luminosities that do not correspond to any single mass or age. When compared to evolutionary models of stars, the pile-up strongly coincides to the phase in their development in which latent heat is predicted to be released in large amounts, resulting in a slowing down of their cooling process. It is estimated that in some cases these stars have slowed down their aging by as much as 2 billion years, or 15 percent of the age of our galaxy.

Dr Tremblay said: "This is the first direct evidence that white dwarfs crystallise, or transition from liquid to solid. It was predicted fifty years ago that we should observe a pile-up in the number of white dwarfs at certain luminosities and colours due to crystallisation and only now this has been observed.

"All white dwarfs will crystallise at some point in their evolution, although more massive white dwarfs go through the process sooner. This means that billions of white dwarfs in our galaxy have already completed the process and are essentially crystal spheres in the sky. The Sun itself will become a crystal white dwarf in about 10 billion years."

Crystallisation is the process of a material becoming a solid state, in which its atoms form an ordered structure. Under the extreme pressures in white dwarf cores, atoms are packed so densely that their electrons become unbound, leaving a conducting electron gas governed by quantum physics, and positively charged nuclei in a fluid form. When the core cools down to about 10 million degrees, enough energy has been released that the fluid begins to solidify, forming a metallic core at its heart with a mantle enhanced in carbon.

Dr Tremblay adds: "Not only do we have evidence of heat release upon solidification, but considerably more energy release is needed to explain the observations. We believe this is due to the oxygen crystallising first and then sinking to the core, a process similar to sedimentation on a river bed on Earth. This will push the carbon upwards, and that separation will release gravitational energy.

"We've made a large step forward in getting accurate ages for these cooler white dwarfs and therefore old stars of the Milky Way. Much of the credit for this discovery is down to the Gaia observations. Thanks to the precise measurements that it is capable of, we have understood the interior of white dwarfs in a way that we never expected. Before Gaia we had 100-200 white dwarfs with precise distances and luminosities - and now we have 200,000. This experiment on ultra-dense matter is something that simply cannot be performed in any laboratory on Earth."

The research was funded by the European Research Council.

** 'Core crystallization and pile-up in the cooling sequence of evolving white dwarfs' in* Nature, *DOI: 10.1038/s41586-018-0791-x*

https://bbc.in/2D9n629

Cheap common drugs may help mental illness

Cheap and widely used drugs for diabetes and heart health have potential for treating severe mental illness, a study hints.

By James Gallagher Health and science correspondent, BBC News

It showed the number of times patients needed hospital treatment fell by up to a fifth when they took the drugs.

The researchers at University College London say their findings have "enormous potential".

But they, and independent experts, say the results now need to be tested in clinical trials.

The starting point for the researchers was a list of currently prescribed medications that science predicts could also help patients with severe mental health disorders.

The team focused on:

- anti-cholesterol drugs called statins - which may calm inflammation linked to mental health problems or help the body absorb anti-psychotic medications
- ***blood pressure drugs - which may alter the calcium signalling in the brain that has been linked to bipolar disorder and schizophrenia***
- ***type 2 diabetes drug metformin - which may alter mood***

But rather than test them in trials, the scientists went looking for evidence in the real world.

They analysed life-long medical records of 142,691 people in Sweden who had schizophrenia, bipolar disorder or other severe mental illnesses.

They then compared the number of times each was admitted to a psychiatric hospital clinic when they were taking those medications and when they were not.

Dr Joseph Hayes, one of the researchers at UCL, said: "The paper suggests a 10-20% reduction in the number of episodes when on the medications rather than off."

The results, published in the journal JAMA Psychiatry, also showed a reduction in self-harm.

"It's incredibly exciting," Dr Hayes said.

"It's got enormous potential and I'm pleased with the way it has turned out.

"But this is really just a starting point."

He wants the drugs to now be tested in large clinical trials, which should give a final answer.

In the meantime, Dr Hayes says people should not go out and try to get the drugs themselves.

But, he says, there are many patients who should be on these drugs for their physical health who are not getting them.

"The thing to do would be to see your GP about full physical health review," Dr Hayes said.

"There's a huge number of people that may benefit from a statin for their heart health and there's a potential knock-on for their mental health, similarly with metformin."

Dr James MacCabe, from the Institute of Psychiatry at King's College London, said: "These findings are very compelling.

"The findings strongly suggest a potential role for repurposing these drugs to improve mental health outcomes."

But there is one nagging doubt, even from the researchers, around the way the study was designed.

A lot of studies compare one group of patients taking a drug with another group not taking it.

This one compared patients at different stages of their life when they were either on the drug or not.

The approach has many advantages but it could mean that when people are in a good place mentally and less likely to be admitted to hospital, they are also more likely to look after themselves and take other medications.

In other words, statins and other drugs could just be a red herring.

This is why Prof Naveed Sattar, from University of Glasgow, remains sceptical and says: "I would be strongly cautious with these findings and would only change my mind if effects are proven to be robust in a randomised trial."

The research group took steps to counter this effect but agree clinical trials are the next step.

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The molecule that helps exercise protect the brain from Alzheimer's

Gives the phrase "muscle memory" a whole new meaning.

Diana Gitig

Sometimes data behaves so nicely, lining up just the way you want it to. In 2012, irisin was identified as a molecular messenger induced by exercise. In 2013, irisin was found to stimulate genes in the hippocampus, a region of the brain essential for making and storing memories. In 2017, epidemiological studies indicated that exercise could slow the development of Alzheimer's disease (AD) and other kinds of dementia. And this week—you guessed it—new research demonstrated that exercise alleviates AD and slows memory loss by sending irisin to the brain.

Irisin is sent from muscles to various tissues throughout the body during exercise. It was initially found to promote fat metabolism, turning white fat cells into brown ones, which burn more energy. It was only later recognized that it also plays a role in the brain.

More than muscle

This new study makes a pretty compelling case that exercise, working through irisin, can protect memories from the neurodegeneration that wreaks such havoc on the minds and lives of Alzheimer's patients. The researchers first showed that irisin levels are lower in the brains of people and mice with AD than in age-matched healthy controls, a correlation that indicated a closer look was called for.

Amyloid β oligomers are toxic protein aggregates that accumulate in Alzheimer's brains and are associated with memory loss. Experiments with cultured rat brain cells, human brain slices, and live mice showed that these amyloid β oligomers are also associated with this decrease of irisin levels in the brain.

Next, the researchers showed that irisin is both necessary and sufficient for protecting memories from degradation. To show that it is necessary, the scientists artificially knocked it down in mouse brains. The mice could no longer recognize a familiar object. To show that it is sufficient, the scientists added extra irisin into the brains of mice and then added amyloid β aggregates. The irisin blocked the memory loss that was caused by the amyloid β aggregates.

Protection

So irisin saves memories from degradation, and irisin is induced by exercise. To fill in the missing step and demonstrate that exercise saves memories via irisin, the researchers put their mice on a strict exercise regimen: an hour of swimming a day, five days a week for five weeks. (Would *you* want to come into the lab on weekends to make your mice swim? Didn't think so.)

As expected, the mice that worked out had higher levels of irisin in their brains than sedentary controls, and their memories were protected from degradation when they got amyloid β oligomers infused into their brains. But the real kicker was that exercise did not help the memories of mice that were infused with an antibody that specifically blocks irisin. This antibody was administered to the circulatory system, indicating that irisin can exert its effects by traveling to the brain during exercise.

The ramifications of these findings range from the coldly clinical to the more grandly philosophical. In the former camp, perhaps low circulating irisin can be used as a biomarker to diagnose and monitor AD, or perhaps the molecule can be administered as a drug to shore up the cognitive abilities of AD patients who are too physically debilitated to reap the other benefits of exercise. In the latter, this link between muscles and memories joins a number of links between the brain and other body parts—notably the gut and the microbiome it harbors. Reductionist views of brain science have not had much success treating Alzheimer's; maybe a more holistic one will.

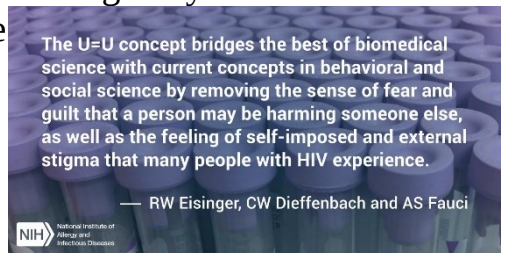
Nature Medicine, 2019. DOI: 10.1038/s41591-018-0275-4 (About DOIs).

http://bit.ly/2Cjmntn

The science is clear: with HIV, undetectable equals untransmittable

NIH officials discuss scientific evidence and principles underlying the U=U concept

WHAT: In recent years, an overwhelming body of clinical evidence has firmly established the HIV Undetectable = Untransmittable (U=U) concept as scientifically sound, say officials from the National Institutes of Health.



Quote from R.W. Eisinger, C.W. Dieffenbach and A.S. Fauci **NIAID**

U=U means that people living with HIV who achieve and maintain an undetectable viral load--the amount of HIV in the blood--by taking and adhering to antiretroviral therapy (ART) as prescribed cannot sexually transmit the virus to others. Writing in *JAMA*, officials from NIH's National Institute of Allergy and Infectious Diseases (NIAID) review the scientific evidence underlying U=U and discuss the implications of widespread acceptance of the message.

In the new commentary, NIAID Director Anthony S. Fauci, M.D., and colleagues summarize results from large clinical trials and cohort studies validating U=U. The landmark NIH-funded HPTN 052 clinical trial showed that no linked HIV transmissions occurred among HIV serodifferent heterosexual couples when the partner living with HIV had a durably suppressed viral load. Subsequently, the PARTNER and Opposites Attract studies confirmed these findings and extended them to male-male couples.

Validation of the HIV treatment as prevention strategy and acceptance of the U=U concept as scientifically sound have numerous behavioral, social and legal implications, the NIAID officials note. U=U can help control the HIV pandemic by preventing HIV transmission, and it can reduce the stigma that many people with HIV face.

The success of U=U as an HIV prevention method depends on achieving and maintaining an undetectable viral load by taking ART daily as prescribed. Numerous factors, including lack of access to quality health care, can make ART adherence difficult. To enhance the overall success of U=U, the authors emphasize the importance of implementing programs that help patients remain in care and address the barriers to daily therapy.

ARTICLE: *RW Eisinger, CW Dieffenbach, AS Fauci. HIV viral load and transmissibility of HIV infection: undetectable equals untransmittable. Journal of the American Medical Association DOI: 10.1001/jama.2018.21167 (2019).*

http://bit.ly/2ClM90q

Experimental antibody 'cocktail' protects animals from three deadly Ebola viruses

Scientists from academia, industry, and government have developed a combination of monoclonal antibodies (mAbs) that protected animals from all three Ebola viruses known to cause human disease.

Their work is described in two companion studies published online in the journal Cell Host & Microbe.

The mAb "cocktail," called MBP134, is the first experimental treatment to protect monkeys against Ebola virus (formerly known as Ebola Zaire), as well as Sudan virus and Bundibugyo virus, and could lead to a broadly effective therapeutic, according to the authors.

Over 20 Ebola virus outbreaks have occurred since the first outbreak was documented in 1976 in the Democratic Republic of Congo, or DRC (formerly called Zaire). The 2013-2016 Ebola epidemic in Western Africa--the largest outbreak to date--sickened more than 28,000 people and caused more than 11,000 deaths. An ongoing outbreak in the eastern Kivu region of DRC is already the second largest on record, according to the World Health Organization.

No Ebola virus medical countermeasures have been approved by the U.S. Food and Drug Administration. An experimental vaccine and several experimental therapeutics--including three based on mAbs--are being studied in the field. Despite their promise, all target only a single Ebola virus (Zaire) and are ineffective against the other two.

"Developing a single treatment that could potentially be used for patients suffering from all the different types of Ebola viruses is an enormous advancement in the field," commented John M. Dye, Ph.D. of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), one of the authors.

Citing growing evidence of the value of monoclonal antibodies for treating even the most virulent infections, Dye added, "This discovery has implications not only for the treatment of Sudan and Bundibugyo viruses, but for newly emerging Ebola viruses as well."

The two mAbs that make up MBP134 were previously discovered by the same research team in the blood of a human survivor of the 2013-2016 outbreak in Western Africa and were shown to target key sites of vulnerability shared by Ebola viruses.

In the first study, a team led by Kartik Chandran, Ph.D., of the Albert Einstein College of Medicine (Einstein) engineered one of the mAbs to improve its activity against Sudan virus. They demonstrated that this enhanced mAb could work especially well with the second naturally occurring mAb to block infection by all three viruses and protect guinea pigs against both Ebola virus and Sudan virus. Additional modification of both mAbs to harness the power of "natural killer" immune cells enhanced MBP134's broad protective efficacy in guinea pigs even further.

In the second study, a team led by Dr. Zachary A. Bornholdt, Ph.D., of Mapp Biopharmaceutical Inc. (MappBio) evaluated the MBP134 cocktail in large animal models that mimic Ebola virus disease in humans more closely. They found that a single low dose of MBP134 could protect monkeys against all three Ebola viruses associated with human disease, even when treatment was begun 4-7 days after the animals were infected.

MBP134 is currently being developed by MappBio in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services, with an indication for Sudan virus.

This work is the product of a public-private partnership between USAMRIID; Einstein; MappBio; Adimab LLC (Lebanon, NH), led by Laura M. Walker, Ph.D.; Public Health Agency of Canada, led by Xiangguo Qiu, Ph.D.; Ragon Institute, led by Galit Alter, Ph.D.; and the University of Texas Medical Branch at Galveston, led by Thomas W. Geisbert, Ph.D.

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UMN Medical School Researchers discover how to treat diastolic heart failure

Research shows magnesium improves a form of heart failure previously without treatment

MINNEAPOLIS, MN - Research out of University Minnesota Medical School and published in the *Journal of Clinical Investigation Insight* uncovers what causes diastolic heart failure and how it can be treated.

In the article, "Magnesium supplementation improves diabetic mitochondrial and cardiac diastolic function," author Samuel Dudley, MD, PhD, Academic Chief of Cardiology at the University of Minnesota Medical School and his fellow researchers found that magnesium can be used to treat diastolic heart failure.

"We've found that cardiac mitochondrial oxidative stress can cause diastolic dysfunction. Since magnesium is an essential element for mitochondrial function, we decided to try the supplement as a treatment," explained Dudley. "It eliminated the poor heart relaxation that causes diastolic heart failure."

Obesity and diabetes are known risk factors for cardiovascular disease. Researchers discovered the magnesium supplement also improved the mitochondrial function and blood glucose in the subjects.

Patients with diastolic heart failure have a high morbidity, mortality, and healthcare costs. Patients with this condition have similar annual mortality to patients with systolic heart failure, and up until now there was no known specific treatments for this type of heart failure.

"This is an exciting step forward in the cardiovascular field," said Dudley, "Right now there are no specific treatments for patients with diastolic heart failure, but now we have a theory of why diastolic heart failure occurs and what we can do to get rid of it."

The next step is human trials. Dudley says this work could also open doors for answers for a related condition, atrial fibrillation.

You can read the article here.

http://bit.ly/2T0m7qc

Woman with Rare Condition Couldn't Hear Male Voices

May seem enviable but could carry serious repercussions

By Mindy Weisberger, Senior Writer

A woman in China suddenly developed an unusual condition that made her unable to hear male voices. And while that might seem enviable to some, the hearing loss could carry serious medical repercussions.

The woman, who is identified only by the surname Chen, visited a hospital after waking up one morning and being unable to hear her boyfriend's voice, Newsweek reported yesterday (Jan. 10). Chen also told doctors that the night before, she experienced ringing in her ears (a condition known as tinnitus) followed by vomiting.

At the hospital, Chen was treated by Dr. Lin Xiaoqing — a woman — who noted that while Chen was able to hear Xiaoqing's voice, she couldn't hear the voice of a nearby male patient "at all," according to

Newsweek. Xiaoqing diagnosed Chen with reverse-slope hearing loss, a rare type of low-frequency hearing loss that likely impaired her ability to hear deep male voices. [Infographic: The Loudest Animals]

Reverse-slope hearing loss (RSHL) gets its name from the shape it produces in visualizations of hearing tests — a slope that is a mirror image of the incline produced by high-frequency hearing loss, according to audiology clinic Audiology HEARS, P.C., in Cumming, Georgia. It affects an estimated 3,000 people in the U.S. and Canada — for every 12,000 people with hearing loss, only one individual has RSHL, the audiology clinic reported.

Humans detect sounds through the vibration of tiny hairs inside the ears, and over time (or because of genetics, injury or drug use) those hairs can become brittle and prone to breakage, said Dr. Michelle Kraskin, an audiologist and the assistant director of hearing and speech for Weill Cornell Medical Center at New York-Presbyterian Hospital in New York City. Kraskin wasn't involved in Chen's case.

The hairs that conduct high-frequency sounds are more delicate and because of this, they're the ones that tend to die first, Kraskin told Live Science. This explains why hearing loss more often affects our ability to hear higher-pitched sounds than lower-pitched ones, she said.

Loss of hearing of lower-pitched sounds (which is what Chen experienced) is also less common because the bass-processing portion of the cochlea — a snail-shaped structure deep in the inner ear — is very well protected, said Jackie Clark, a clinical professor with the School of Behavioral and Brain Sciences at the University of Texas at Dallas, who also wasn't involved with Chen's case.

Causes of the sudden onset of RSHL can include blood vessel problems or trauma, Clark told Live Science. Autoimmune disorders that affect the inner ear — which are thought to occur in about 1 percent of the U.S. population — may also be a cause of RSHL, Clark said. Indeed, autoimmune conditions in the inner ear can cause balance problems that may lead to vomiting — a symptom that Chen described to her doctor, Clark noted.

Though it might be amusing to imagine a world in which male voices are nonexistent, hearing loss is no laughing matter, Clark said. People who experience sudden and unexplained hearing loss should see a specialist as soon as possible.

The good news is that when RSHL is detected quickly, chances are good that the hearing loss can be reversed, Kraskin said.

"Most studies have shown that if you catch it within 48 hours, you have the best chance for recovery," she said. Treatment can involve high doses of steroids, but sometimes the condition goes away without any treatment whatsoever, she added.

In Chen's case, her doctor said that stress from working late and losing sleep caused Chen's low-frequency hearing decline, adding that rest would soon fully restore the woman's hearing, Newsweek reported.

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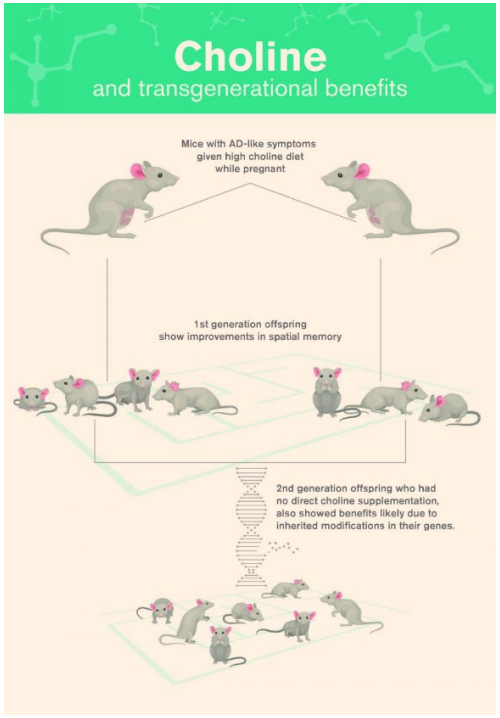
Choline: Vitamin-Like Nutrient May Help Protect against Alzheimer's Disease

Offspring of mice given high choline in their diet show improvements in spatial memory

by News Staff / Source

The prevalence of Alzheimer's disease (AD) is anticipated to increase significantly over the next few decades. This is alarming given that no effective treatment options are available to prevent, treat, or manage AD. Thus, there is an urgent need to develop new therapeutic approaches to mitigate this memory-stealing disorder. In a study published in the journal* Molecular Psychiatry, *researchers tested the transgenerational benefits of maternal supplementation of choline, an important nutrient that may hold promise in the war against the disorder, in two generations of AD model mice. The results showed that when AD mice are given

high choline in their diet, their offspring show improvements in spatial memory, compared with those receiving a normal choline regimen in the womb.



Choline is a vitamin-like essential nutrient that is naturally present in some foods and also available as a dietary supplement. It is a source of methyl groups needed for many steps in metabolism. All plant and animal cells require choline to maintain their structural integrity. This compound is used by the body to produce acetylcholine, an important neurotransmitter essential for brain and nervous system functions including memory, muscle control and mood. Choline also plays a vital role in regulating gene expression.

Mice with AD-like symptoms receiving supplemental levels of choline in the womb improved their spatial memory. A second generation bred from these choline-treated mice also showed improved spatial memory, suggesting epigenetic changes in genes. Choline acts to reduce harmful levels of the amino acid homocysteine, converting it to the beneficial chemical methionine. **Shireen Dooling, Biodesign Institute at Arizona State University.**

It has long been recognized that choline is particularly important in early brain development.

Pregnant women are advised to maintain choline levels of 550 mg per day for the health of their developing fetus.

“There’s a twofold problem with this,” said study first author Dr. Ramon Velazquez, a researcher at Arizona State University.

“Studies have shown that about 90% of women don’t even meet that requirement.”

“Choline deficits are associated with failure in developing fetuses to fully meet expected milestones like walking and babbling. But we show that even if you have the recommended amount, supplementing with more in a mouse model gives even greater benefit.”

Indeed, when the AD mice received supplemental choline in their diet, their offspring showed significant improvements in spatial memory, which was tested in a water maze.

Subsequent examination of mouse tissue extracted from the hippocampus, a brain region known to play a central role in memory formation, confirmed the epigenetic alterations induced by choline supplementation.

Modified genes associated with microglial activation and brain inflammation, and reduced levels of an amino acid called homocysteine resulted in the observed performance improvements in spatial memory tasks.

Due to the epigenetic modifications induced by choline, the improvements carried over to the offspring of mice receiving supplemental choline in the womb. “Choline acts to protect the brain from AD in at least two ways,” the researchers explained.

“First, choline reduces levels of homocysteine. This amino acid is known to double the risk of developing AD and is found in elevated levels in patients with AD. Choline performs a chemical transformation, converting the harmful homocysteine into the helpful chemical methionine.”

“This conversion happens thanks to an enzyme known as betaine-homocysteine methyltransferase (BMHT).”

Dr. Velazquez and colleagues found that choline supplementation increased the production of BMHT in two generations of mice.

“Secondly, choline supplementation reduces the activation of microglia — cells responsible for clearing away debris in the brain,” they said.

"While their housekeeping functions are essential to brain health, activated microglia can get out of control, as they typically do during AD. Over-activation of microglia causes brain inflammation and can eventually lead to neuronal death. Choline supplementation reduces the activation of microglia, offering further protection from the ravages of AD."

Ramon Velazquez et al. *Maternal choline supplementation ameliorates Alzheimer's disease pathology by reducing brain homocysteine levels across multiple generations.* Molecular Psychiatry, *published online January 8, 2019; doi: 10.1038/s41380-018-0322-z*