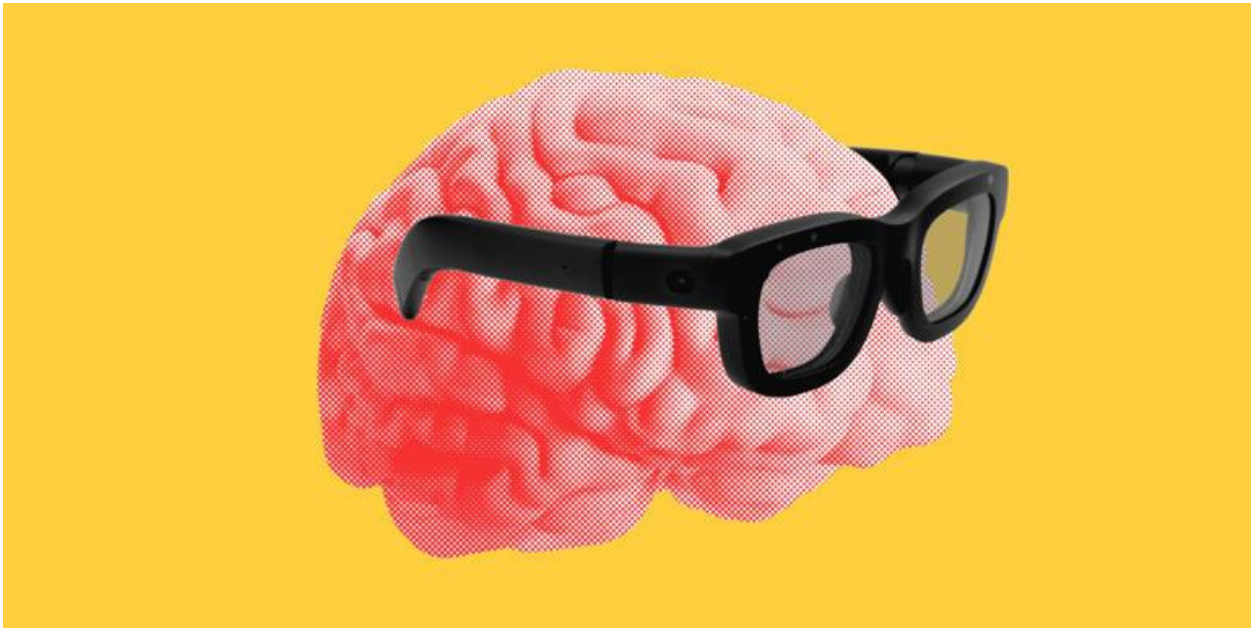
BRAIN INTRACRANIAL VOL 2



Meta has launched the world's 'most advanced' glasses. Will they replace smartphones?

Humans are increasingly engaging with wearable technology as it becomes more adaptable and interactive. One of the most intimate ways gaining acceptance is through augmented reality (AR) glasses.

Last week, Meta debuted a prototype of the most recent version of their AR glasses—Orion. They look like reading glasses and use holographic projection to allow users to see graphics projected through transparent lenses into their field of view.

Meta chief Mark Zuckerberg called Orion "the most advanced glasses the world has ever seen." He said they offer a "glimpse of the future" in which smart glasses will replace smartphones as the main mode of communication.

But is this true or just corporate hype? And will AR glasses actually benefit us in new ways?

Old technology, made new

The technology used to develop Orion glasses is not new.

In the 1960s, computer scientist Ivan Sutherland introduced the first augmented reality head-mounted display. Two decades later, Canadian engineer and inventor Stephen Mann developed the first glasses-like prototype.

Throughout the 1990s, researchers and technology companies developed the capability of this technology through head-worn displays and wearable computing devices. Like many technological developments, these were often initially focused on military and industry applications.

In 2013, after smartphone technology emerged, Google entered the AR glasses market. But consumers were disinterested, citing concerns about privacy, high cost, limited functionality and a lack of a clear purpose.

This did not discourage other companies—such as Microsoft, Apple and Meta—from developing similar technologies.

Looking inside

Meta cites a range of reasons for why Orion are the world's most advanced glasses, such as their miniaturized technology with large fields of view and holographic displays. It said these displays provide: "compelling AR experiences, creating new human-computer interaction paradigms [...] one of the most difficult challenges our industry has ever faced."

Orion also has an inbuilt smart assistant (Meta AI) to help with tasks through voice commands, eye and hand tracking, and a wristband for swiping, clicking and scrolling.

With these features, it is not difficult to agree that AR glasses are becoming more user-friendly for mass consumption. But gaining widespread consumer acceptance will be challenging.

A set of challenges

Meta will have to address four types of challenges:

1. ease of wearing, using and integrating AR glasses with other glasses
2. physiological aspects such as the heat the glasses generate, comfort and potential vertigo
3. operational factors such as battery life, data security and display quality
4. psychological factors such as social acceptance, trust in privacy and accessibility.

These factors are not unlike what we saw in the 2000s when smartphones gained acceptance. Just like then, there are early adopters who will see more benefits than risks in adopting AR glasses, creating a niche market that will gradually expand.

Similar to what Apple did with the iPhone, Meta will have to build a digital platform and ecosystem around Orion.

This will allow for broader applications in education (for example, virtual classrooms), remote work and enhanced collaboration tools. Already, Orion's holographic display allows users to overlay digital content and the real world, and because it is hands-free, communication will be more natural.

Creative destruction

Smart glasses are already being used in many industrial settings, such as logistics and health care. Meta plans to launch Orion for the general public in 2027.

By that time, AI will have likely advanced to the point where virtual assistants will be able to see what we see and the physical, virtual and artificial will co-exist. At this point, it is easy to see that the need for bulky smartphones may diminish and that through creative destruction, one industry may replace another.

This is supported by research indicating the virtual and augmented reality headset industry will be worth US$370 billion by 2034.

The remaining question is whether this will actually benefit us.

There is already much debate about the effect of smartphone technology on productivity and well-being. Some argue that it has benefited us, mainly through increased connectivity, access to information, and productivity applications.

But others say it has just created more work, distractions and mental fatigue.

If Meta has its way, AR glasses will solve this by enhancing productivity. Consulting firm Deloitte agrees, saying the technology will provide hands-free access to data, faster communication and collaboration through data-sharing.

It also claims smart glasses will reduce human errors, enable data visualization, and monitor the wearer's health and well-being. This will ensure a quality experience, social acceptance, and seamless integration with physical processes.

But whether or not that all comes true will depend on how well companies such as Meta address the many challenges associated with AR glasses.

Neuroscience Says Your Brain Craves 'New' For the Dopamine Rush, but Research Shows You Can Replace That Sensation Much More Productively

New products and ideas can be attractive because they're exciting to discover. But they can also make it less likely you'll achieve your actual goal.

A friend hates keeping his books. (He hates filing corporate taxes even more, but that's another story.) Over the past three years, he's adopted and abandoned five different small-business accounting packages--not because the software didn't work, but because he kept finding newer, shinier, more robust tools that he felt sure would solve all his problems.

Except they didn't. Accounting is still accounting, and he's still him. But that's also because he--and we--are made that way.

A study published in *Neuron* found that dopaminergic novelty processing (a fancy way of saying your brain lights up when you encounter something new) makes a new product or service--or new diet, new workout plan, new longevity enhancement breakthrough, etc.-- hard to resist.

As a corollary, the more complicated something sounds--like a comprehensive, multi-step morning routine--the more likely we are to believe it will work, even though science shows simple is always better.

Add it all up, and we're built to shrug off the commonplace. Same stuff, different day might work, but it's also neurologically boring. Our hippocampi love the dopamine rush that comes from finding a new approach.

They especially love the dopamine rush that comes from finding a new, and extreme, approach--even though the more extreme and complicated the approach, the less likely you'll embrace it over the long term.

My friend cares about cash flow, but running discounted cash flow models? Not so much. He cares about profitability, but he has no interest in reviewing sensitivity models, much less in creating them. He's successful because he's the king of sales, cash flow, and profitability -- not esoteric (to him) financial reports.

In short, he doesn't need "new," even though his hippocampus tells him he does. He needs simple, reliable, and easy-to-use.

And so do you. New can be better, but new without purpose is not. Productive people don't just know what to do--they know *why*. They have long-term goals. They have short-term goals that support their long-term goals. In short, they have purpose--and that purpose informs everything they do.

That's why productive people appear so dedicated, organized, and consistently on-task. They're not slaves to a routine, nor are they slaves to the occasional dopamine rush that comes from considering something new.

They're just driven to reach their goals, and quick to eliminate roadblocks and put aside distractions that stand in their way.

If you're an entrepreneur, your goal is to build a successful business. Your system--and your tools--are your processes for sales, marketing, fulfillment, operations, etc. Already have something that works? Great. Embrace it. Enhance it. Optimize it.

And seek your dopamine rushes elsewhere. In simple terms, dopamine is a reward your brain releases when you've achieved--or are close to achieving--a goal, helping you feel more motivated and satisfied.

A Harvard nutritionist and a neuroscientist agree this is the No. 1 food for a healthy brain© Provided by CNBC

What you eat can, and does, impact the function of your brain, including your ability to ward off Alzheimer's disease and there are certain foods — like sunflower seeds and whole grains — that provide greater benefits.

There is one food in particular that Dr. Uma Naidoo, a Harvard nutritionist, and Lisa Genova, a Harvard-trained neuroscientist, say is the key to a healthy brain: Green leafy vegetables.

DON'T MISS:** **5 doctors and nutritionists share the foods they eat every day for brain health, longevity and overall wellness

The No. 1 food for a healthy brain: Green leafy vegetables

Across the board, experts agree that eating leafy greens is essential for overall health, especially for your brain.

Some of the green leafy vegetables that you can add to your meals are:

- Kale
- Spinach
- Lettuces
- Cabbage
- Swiss chard

- Bok choy
- Mustard greens

3 reasons experts say a diet rich in leafy greens is good for your brain

1. They're rich in B vitamins

Often, conditions like depression and dementia are associated with a vitamin B deficiency, according to a study from the Wayne State University School of Medicine.

Green leafy vegetables are a wonderful source of vitamin B9, Naidoo told CNBC Make It in 2022. The vitamin, also known as folate, is "a key vitamin for supporting brain and neurological health, optimal neurotransmitter function, and balanced psychological health," she added.

Leafy greens are the first type of food that Naidoo suggests for her patients who are looking to boost their mood.

2. They're high in brain-boosting nutrients

Green leafy vegetables are also full of what Genova calls "brain-boosting nutrients" including folate, lutein and beta-carotene.

Lutein has been linked to an improvement in brain function and brain structure for older adults. And a systematic review found that taking beta-carotene supplements can boost "verbal and cognitive memory."

3. They're full of fiber

Increasing intake of dietary fiber was associated with a lower chance of developing depression, a study published in "Complementary Therapies in Medicine" in 2021 found.

Naidoo prefers to recommend getting more fiber through your diet, specifically plant-based foods. And leafy greens just so happen to be fiber-dense.

The Hunt For The Laws Of Physics Behind Memory And Thought

One of the curious features of the laws of physics is that many of them seem to be the result of the bulk behavior of many much smaller components. The atoms and molecules in a gas, for example, move at a huge range of velocities. When constrained in a container, these particles continually strike the surface creating a force.

But it is not necessary to know the velocities of all the particles to determine this force. Instead, their influence averages out into a predictable and measurable bulk property called pressure.

This and other bulk properties like temperature, density and elasticity, are hugely useful because of the laws of physics that govern them. Over one hundred years ago, physicists like Willard Gibbs and others determined the mathematical character of these laws and the statistical shorthand that physicists and engineers now use routinely in everything from laboratory experiments to large scale industrial processes.

The success of so-called statistical physics raises the possibility that other systems that consist of enormous numbers of similar entities might also have their own "laws of physics". In particular, physicists have long hoped that the bulk properties of neurons might be amenable to this kind of approach.

Neural Physics

The behavior of single neurons is well understood. But put them together into networks and much more significant behaviors emerge, such as sensory perception, memories and thought. The hope is that a statistical or mathematical approach to these systems could reveal the laws of neural physics that describe the bulk behavior of nervous systems and brains.

"It is an old dream of the physics community to provide a statistical mechanics description for these and other emergent phenomena of life," say Leenoy Meshulam at the University of Washington and William Bialek at Princeton University, who have reviewed progress in this area.

"These aspirations appear in a new light because of developments in our ability to measure the electrical activity of the brain, sampling thousands of individual neurons simultaneously over hours or days."

The nature of these laws is, of course, fundamentally different to the nature of conventional statistical physics. At the heart of the difference is that neurons link together to form complex networks in which the behavior of one neuron can be closely correlated with the behavior of its neighbors.

It is relatively straightforward to formulate a set of equations that capture this behavior. But it quickly becomes apparent that these equations cannot be easily solved in anything other than trivial circumstances.

Instead, physicists must consider the correlations between all possible pairs of neurons and then use experimental evidence to constrain what correlations are possible.

The problem, of course, is that the number of pairs increases exponentially with the number of neurons. That raises the question of how much more data must be gathered to constrain the model as the number of neurons increases.

One standard system in which this has been well measured is the retina. This consists of a network of light sensitive neurons in which activity between neighbors is known to be corelated. So if one neuron is activated there is a strong possibility that its neighbor will be too. (This is the reason for the gently evolving, coral-like patterns in vision that people sometimes notice when they first wake up.)

Experiments in this area began by monitoring the behavior of a handful of neurons, then a few dozen, a few hundred and now approach thousands (but not millions). It turns out that the data helps constrain the model to the point where they give remarkably accurate predictions of neural behavior when asked, for example, to predict how many neurons are active out of any given set of them.

That suggests the system of equations accurately captures the behavior of retinal networks. In other words, "the models really are the solutions to the mathematical problem that we set out to solve," say Meshulam and Bialek.

Of course, the retina is a highly specialized part of the nervous system so an important question is whether similar techniques can generalize to the higher cognitive tasks that take place in other parts of the brain.

Emergent Behavior

One challenge here is that networks can demonstrate emergent behavior. This is not the result of random correlations or even weak correlations. Instead, the correlations can be remarkably strong and can spread through a network like an avalanche.

Networks that demonstrate this property are said to be in a state of criticality and are connected in a special way that allows this behavior. This criticality turns out to be common in nature and suggests networks can tune themselves in a special way to achieve it.

"Self-organized criticality" has been widely studied in the last two decades and there has been some success in describing it mathematically. But exactly how this self-tuning works is the focus of much ongoing research.

Just how powerful these approaches will become is not yet clear. Meshulam and Bialek take heart from the observation that some natural behaviors are amenable to the kind of analysis that physicists are good at. "All the birds in a flock agreeing to fly in the same direction is like the alignment of spins in a magnet," they say.

The fact that this is merely a metaphor concerns them - metaphors can help understanding but the real behavior of these system is often much more complex and subtle.

But there are reasons to think that mathematical models can go further. "The explosion of data on networks of real neurons offers the opportunity to move beyond metaphor," they say, adding that the data from millions of neurons should soon help to inform this debate.

"Our experimentalist friends will continue to move the frontier, combining tools from physics and biology to make more and more of the brain accessible in this way," conclude Meshulam and Bialek. "The outlook for theory is bright."

Ref: Statistical mechanics for networks of real neurons : arxiv.org/abs/2409.00412

Harvard nutritionist's guide to the No. 1 brain-boosting nutrient and the best ways to consume it© Provided by CNBC

There is no one-size-fits-all way to prevent dementia. That said, a vast number of studies have isolated certain nutrients that may help prevent the loss of cognitive functioning with age, like perception, attention and decision making.

Three types of neuroprotective nutrients have received the most interest from experts like myself: antioxidants, B vitamins, and polyunsaturated fatty acids. Antioxidants combat free radicals that can damage brain cells, B vitamins play an important role in brain cell function, and PUFAs help promote the growth of new brain cells.

While supplements can help provide these nutrients, I always tell people to first go to real foods, especially for fatty acids like omega-3s. When you eat a whole food you get additional vitamins, minerals, healthy fats, and protein. It's a good foundation upon which to build a healthy eating plan.

Omega-3 fatty acids are the No. 1 nutrient for a healthy brain

Omega-3s are found in wild-caught fatty fish like anchovies, sardines, and salmon. Wild Sockeye salmon in particular contains levels of EPA and DHA that are beneficial to our brain's health.

An average salmon filet in the U.S. is about three to four ounces and the suggested amount to eat per week is about eight. So one should try to get Omega-3-rich fish onto your plate at least twice a week.

If you are like me and don't eat seafood (I was raised vegetarian), you may be relieved to know it is still possible to get adequate omega-3s from plant-based sources, including:

- Chia seeds
- Sesame seeds
- Walnuts
- Flax seeds

About one ounce of chia seeds is more than your daily recommended intake of omega-3 fatty acids and delivers about 5,000 mg.

If you eat eggs, aim for the pasture-raised kind. Be sure to add turmeric with a pinch of black pepper to optimize the impact for brain health.

It's important to underline that we can't out-supplement or exercise our way out of a poor diet. An overall healthy lifestyle with good nutrition, alongside regular exercise, proper sleep, mindfulness, social connections, stress management and lower anxiety, are critical factors to fend off conditions like dementia.

Dr. Uma Naidoo is a Harvard-trained nutritional psychiatrist, professional chef, and nutritional biologist. She is also the author of the bestselling "This is Your Brain on Food" and most recently, "Calm Your Mind with Food." Follow her on Instagram or subscribe to her newsletter on Substack.

Deep brain stimulation may provide immediate improvement in arm and hand strength and function weakened by traumatic brain injury or stroke, University of Pittsburgh School of Medicine researchers report today in *Nature Communications*.

Encouraging results from extensive tests in monkeys and humans open a path for a new clinical application of an already widely used brain stimulation technology and offer insights into neural mechanisms underlying movement deficits caused by brain injury.

"Arm and hand paralysis significantly impacts the quality of life of millions of people worldwide," said senior and corresponding author Elvira Pirondini, Ph.D., assistant professor of physical medicine and rehabilitation at Pitt. "Currently, we don't have effective solutions for patients who suffered a stroke or traumatic brain injury, but there is a growing interest in the use of neurotechnologies that stimulate the brain to improve upper-limb motor functions."

Brain lesions caused by serious brain trauma or stroke can disrupt neural connections between the motor cortex, a key brain region essential for controlling voluntary movement, and the muscles. Weakening of these connections prevents effective activation of muscles and results in movement deficits, including partial or complete arm and hand paralysis.

To boost the activation of existing but weakened connections, researchers proposed using deep brain stimulation (DBS), a surgical procedure that involves placing tiny electrodes in specific areas of the brain to deliver electrical impulses that regulate abnormal brain activity. Over the past several decades, DBS has revolutionized the treatment of neurological conditions such as Parkinson's disease by providing a way to control symptoms that were once difficult to manage with medication alone.

"DBS has been life-changing for many patients. Now, thanks to ongoing advancements in the safety and precision of these devices, DBS is being explored as a promising option for helping stroke survivors recover their motor functions," said senior author and surgical leader of the project, Jorge González-Martínez, M.D., Ph.D., professor and vice-chair of neurosurgery and director of the epilepsy

and movement disorders program at Pitt. "It offers new hope to millions of people worldwide."

Taking cues from another successful Pitt project that used electrical stimulation of the spinal cord to restore arm function in individuals affected by stroke, scientists hypothesized that stimulating the motor thalamus—a structure nested deep in the brain that acts as a key relay hub of movement control—using DBS could help restore movements that are essential for tasks of daily living, such as object grasping.

However, because the theory has not been tested before, they first had to test it in monkeys, which are the only animals that have the same organization of the connections between the motor cortex and the muscles as humans.

To understand the mechanism of how DBS of the motor thalamus helps improve voluntary arm movement and to finesse the specific location of the implant and the optimal stimulation frequency, researchers implanted the FDA-approved stimulation device into monkeys that had brain lesions affecting how effectively they could use their hands.

As soon as the stimulation was turned on, it significantly improved activation of muscles and grip force. Importantly, no involuntary movement was observed.

To verify that the procedure could benefit humans, the same stimulation parameters were used in a patient who was set to undergo DBS implantation into the motor thalamus to help with arm tremors caused by brain injury from a serious motor vehicle accident that resulted in severe paralysis in both arms.

As soon as the stimulation was turned on again, the range and strength of arm motion was immediately improved. The participant was able to lift a moderately heavy weight and reach, grasp and lift a drinking cup more efficiently and smoothly than without the stimulation.

To help bring this technology to more patients in the clinic, researchers are now working to test the long-term effects of DBS and determine whether chronic stimulation could further improve arm and hand function in individuals affected by traumatic brain injury or stroke.

Other authors of this research are Jonathan Ho, B.S., Erinn Grigsby, Ph.D., Arianna Damiani, M.S., Lucy Liang, M.S., Josep-Maria Balaguer, M.S., Sridula Kallakuri, Lilly Tang, B.S., Jessica Barrios-Martinez, M.D., Vahagn Karapetyan, M.D., Ph.D., Daryl Fields, M.D., Ph.D., Peter Gerszten, M.D., T. Kevin Hitchens, Ph.D., M.B.A., Theodora Constantine, P.A.-C., Gregory Adams, B.S., Donald Crammond, Ph.D., and Marco Capogrosso, Ph.D., all of Pitt.

More information: *Nature Communications* (2024). DOI: 10.1038/s41467-024-52477-1. www.nature.com/articles/s41467-024-52477-1

You might already know about the benefits of specific nutrients — like vitamin A in carrots for eye health or calcium in dairy products for strong bones — but nutrients that support brain health often receive less attention. Yet the brain is vital for everything from memory and mood to managing stress, so it's essential to keep it well-nourished.

Here are the best foods to support your brain and the nutrients that make them so beneficial — with the bonus that they can also help with weight loss.

1. Fatty Fish

Salmon, herring, whitefish, and anchovies top the Cleveland Clinic's list of brain-boosting fatty fish, packed with omega-3s like DHA and EPA. Maggie Moon, a Los Angeles–based registered dietitian and author of *The MIND Diet: 2nd Edition*, shares that these omega-3s protect the brain from inflammation linked to cognitive decline, Alzheimer's disease, and depression.

Research shows that omega-3 fatty acids may improve learning, memory, and cognitive well-being by enhancing blood flow in the brain. "This translates into how well the brain thinks, learns, and remembers," says Moon. DHA also benefits mental health from early childhood into adulthood, according to research.

“Seafood is an excellent lean protein choice for people who want to make the most of their calories while losing weight, including salmon and tuna, two of the most accessible fatty fish popular in the U.S.,” says Moon. The American Heart Association recommends eating fish twice a week, and the Dietary Guidelines for Americans from the U.S. Department of Agriculture (USDA) advise at least 8 ounces of seafood per week based on a 2,000-calorie diet. But for those just getting started, Moon suggests eating fatty fish once a week, and building from there.

2. Dark Chocolate

If you’re a chocolate lover, you may be happy to know that dark chocolate has brain-boosting benefits. Research shows dark chocolate is rich in flavonoids, a type of antioxidant that may positively impact cognitive performance. Another study suggests dark chocolate may reduce both mental and physical fatigue, which can enhance overall vitality, allow for better executive function, improve memory, and increase gray matter volume in the brain.

Moon says if you’re looking for the highest flavonoid content from a cacao bean, taking a cocoa flavonol supplement or eating cacao nibs, which have no sugar, are best. “Otherwise, the best thing to do is seek out the highest percentage of dark chocolate your palate enjoys,” says Moon. She says dark chocolate is commonly available at 60 to 85 percent cocoa, and the higher the percentage, the more beneficial bioactives it contains. Moon notes that higher cocoa levels also generally mean less added sugar and saturated fat, which can be helpful for weight loss, though it will taste more bitter.

3. Seeds

Certain seeds, like flaxseeds and chia seeds, are packed with omega-3 fatty acids in the form of alpha-linolenic acid (ALA). The National Institutes of Health says the body can’t make this fatty acid on its own, so you must get ALA from your diet.

Bryan Quoc Le, PhD, food scientist and author of *150 Food Science Questions Answered: Cook Smarter, Cook Better*, from Puyallup, Washington, says "during the early development of the brain, ALA serves as an important structural component for brain tissue." Research confirms that eating chia seeds may support healthy brain development. This is also seen with flaxseeds; research credits them with helping to protect the brain from diseases, ease depression, and reduce stress-related damage. Dr. Le adds that ALA, found in seeds, may even boost a protein called BDNF, which research indicates can aid learning and memory.

Chia seeds and flaxseeds both contribute greatly to a high-fiber diet — which research ties to weight loss by way of improved metabolism, lowered hunger hormones, and increased satiety. Chia seeds offer 5 grams (g) of dietary fiber per tablespoon, per the USDA, while flaxseeds add 2 g of dietary fiber per tablespoon, according to the USDA.

Work seeds into your weight-loss meal prep with tasty overnight chia pudding and almond butter flaxseed granola bars.

4. Blueberries

Blueberries are packed with anthocyanins, which Le says protect brain cells and give the fruit its blue color. According to Le, the brain's high energy use can create harmful byproducts, but the antioxidants in blueberries help neutralize them to keep the brain healthy. Research supports this and further explains that anthocyanins may help prevent or treat brain disorders like Alzheimer's and Parkinson's diseases.

Other research shows that eating more blueberries (or anthocyanins) helps reduce the risk of cardiovascular disease, type 2 diabetes, and death, as well as promotes a healthy weight and mind. "Blueberries have a very low glycemic index, low sugar, and high fiber," says Le, who recommends eating them freely — like in smoothies, whole-grain muffins, or high-protein pancakes.

5. Leafy Greens

"I always recommend eating more leafy green vegetables for brain health," says Moon. The MIND diet, known for its brain-boosting benefits, includes a specific recommendation to eat leafy greens at least six times a week. Research shows that following this diet can reduce the risk of Alzheimer's disease by up to 53 percent and keep the brain about 7.5 years younger.

Moon cited a study showing that older adults who regularly ate leafy greens, especially those from the cabbage family like bok choy, had cognitive abilities equivalent to being 11 years younger compared to those who rarely ate them.

"We always have a big box of prewashed salad greens in our refrigerator, which makes it easy to add a big handful of greens to meals, snacks, and smoothies throughout the day," says Moon. Plus, 3 ounces of arugula contain just 20 calories, according to the USDA, making it a great low-calorie option for weight loss, too.

The Wrap-Up

A varied diet plays a crucial role in brain health, with omega-3s and antioxidants being particularly vital. Fatty fish, dark chocolate, seeds, blueberries, and leafy greens deliver nutrients that drive brain development and function. Incorporating these foods into meals or snacks nourishes the body, fuels the brain, and aligns with weight loss goals.

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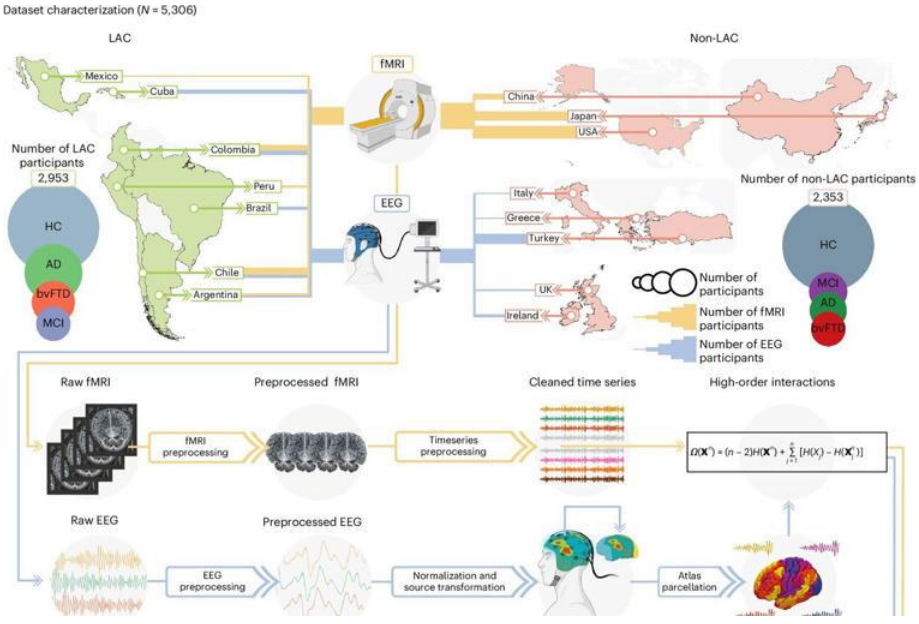

Dataset characterization and analysis pipeline. Credit: Nature Medicine (2024). DOI: 10.1038/s41591-024-03209-x

The pace at which the brain ages can vary significantly among individuals, leading to a gap between the estimated biological age of the brain and the chronological age (the actual number of years a person has lived).

This gap may be influenced by various factors, including physical (e.g. pollution) and social (e.g. socioeconomic or health inequalities) exposomes, especially in aging and dementia. Until now, it was unclear how these combined factors could either accelerate or delay brain aging across diverse geographical populations.

Now, in a trailblazing study published in *Nature Medicine*, researchers at the Global Brain Health Institute at Trinity College Dublin led a wider team of international colleagues to develop innovative measures of brain aging using advanced brain clocks based on deep learning of brain networks.

This study involved a diverse dataset of 5,306 participants from 15 countries, including participants from the US, Latin America (LAC), Europe, and Asia.

Data from Ireland was integrated with other EU countries for the study. By analyzing data from functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), the researchers quantified brain age gaps in healthy individuals and those with neurodegenerative conditions such as mild cognitive impairment (MCI), Alzheimer's disease, and frontotemporal lobe degeneration (FTLD).

The study revealed that populations from countries with greater inequalities generally exhibited older brain ages. This effect was shown in a large, geographically diverse sample, including participants from high-income and low- to middle-income countries. This accelerated aging was particularly evident in brain regions most vulnerable to aging, specifically those involving frontoposterior networks.

The study found that structural socioeconomic inequality, air pollution, and the burden of communicable and non-communicable diseases were significant predictors of increased brain age gaps, especially in more disadvantaged countries. Participants with a diagnosis of dementia, particularly Alzheimer's disease, exhibited the most critical brain age gaps.

The research also highlighted sex differences in brain aging, with women in LAC countries showing greater brain age gaps, particularly in those with Alzheimer's disease. These differences were linked to biological sex and gender disparities in health and social conditions. These findings underscore the role of environmental and social exposomes in brain health disparities.

The results of this study have profound implications for neuroscience and brain health, particularly in understanding the interaction between macro factors (exposome) and the mechanisms that underlie brain aging across diverse populations in healthy aging and dementia.

The study's approach, which integrates multiple dimensions of diversity into brain health research, offers a new framework for personalized medicine. This framework could be crucial for identifying individuals at risk of neurodegenerative diseases and developing targeted interventions to mitigate these risks.

Moreover, the study's results highlight the importance of considering the biological embedding of environmental and social factors in public health policies. Policymakers can reduce brain age gaps and promote healthier aging across populations by addressing issues such as socioeconomic inequality and environmental pollution.

Agustin Ibanez, corresponding and leading author, is Professor in Brain Health at the Global Brain Health Institute (GBHI) at Trinity, and School of Medicine, Trinity, and Director of the Latin American Brain health Institute (BrainLat). He said, "Your brain's age isn't just about years—it's about where and how you live. The innovative use of computational neuroscience tools across a large, diverse sample has provided valuable insights into how different exposures can induce accelerated or delayed brain aging—an essential consideration for policymakers."

More information: Sebastian Moguilner et al, Brain clocks capture diversity and disparities in aging and dementia across geographically diverse populations, *Nature Medicine* (2024). DOI: 10.1038/s41591-024-03209-x

(Photo credit: DALL·E)© PsyPost

A recent study published in *Nature Aging* has shown that it is possible to reverse age-related slowing of brain waste clearance, a key process that may contribute to neurological diseases like Alzheimer's and Parkinson's. Using a drug already approved for clinical use, researchers were able to restore this waste-clearing function in older mice, bringing it back to the efficiency seen in younger brains. The findings offer a potential pathway for developing treatments that target brain waste removal, which could delay or mitigate the effects of age-related neurological disorders.

Neurological diseases such as Alzheimer's and Parkinson's are often linked to the accumulation of toxic proteins in the brain. Over time, these proteins build up due to a failure of the brain's waste removal system, which clears out harmful substances. In younger individuals, this system, known as the glymphatic system, works efficiently to wash away these toxic proteins using cerebrospinal fluid (CSF). However, as people age, the brain's ability to clear out waste slows down, increasing the risk of diseases associated with this toxic buildup.

Researchers have long suspected that the lymphatic system—the network of vessels that remove waste from the body—may play a critical role in this process. Specifically, lymph vessels in the neck are believed to help remove CSF loaded with waste from the brain. But as the body ages, these vessels lose their ability to function properly. This study aimed to determine whether it was possible to restore their function and, by extension, the brain's waste removal capabilities.

"The circulation of water-like fluid through and around brain tissue clears away wastes whose buildup correlates with diseases like Alzheimer's and Parkinson's. Those diseases are more likely in older patients, and many studies have shown that waste is cleared more slowly in older animals. We wondered if the lymph vessels in the neck, which take fluid from the skull, might play a role, and if we could counteract some effects of aging," said Douglas H. Kelley, a professor of mechanical engineering at the University of Rochester.

To investigate, the researchers focused on a particular set of lymph vessels in the neck, known as cervical lymph vessels. These vessels drain approximately half of

the brain's waste-laden cerebrospinal fluid into the body's lymphatic system, where it is ultimately processed and eliminated. The study used advanced imaging techniques to observe and measure how efficiently these vessels worked in younger and older mice.

The researchers tracked the flow of CSF from the brain through the cervical lymph vessels, paying close attention to the way the vessels pulsed, which helps to pump the fluid. In young mice, the vessels contracted regularly and efficiently, but in older mice, the vessels were less active, contracting less frequently and with reduced strength. This resulted in a 63% slowdown in the removal of CSF from the brain in older mice compared to younger ones.

After documenting the decline in function, the research team wanted to see if they could restore the activity of these aging lymph vessels. They used a drug called prostaglandin F2 alpha, a hormone-like compound that stimulates smooth muscle contractions. This drug is already in medical use to induce labor and has a known effect on smooth muscle tissue, which lines the lymph vessels.

By applying prostaglandin F2 alpha to the cervical lymph vessels, the researchers were able to restore the vessels' ability to pump CSF out of the brain as efficiently as in younger animals. This finding suggests that it may be possible to develop treatments that target this mechanism, potentially offering a way to slow or prevent the buildup of toxic proteins in the brain and delay the onset of neurological diseases.

"As mice get older, neck lymph vessels don't work as well to clear brain waste, but a muscle-stimulating drug (prostaglandin 4 alpha) can make old vessels pump fluid as well as young ones," Kelley told PsyPost. "Personally, I was surprised and impressed that the effect of the drug was so strong!"

While the study offers promising insights into how brain waste clearance might be restored in aging populations, there are several important limitations to consider. The study was conducted in mice, and it is unclear whether the same results would apply to humans. While the underlying mechanisms of brain waste clearance and lymph vessel function are likely to be similar, further research will be necessary to confirm whether the same approach would work in people.

"We worked only with mice, so many more trials will be necessary before human patients see similar treatments," Kelley noted. "We applied the drug directly to

the lymph vessels, during surgery, so developing an ointment, pill, or injection would make it more convenient."

Additionally, while the drug successfully restored lymph vessel function in the study, it is unclear how long the effects would last or whether repeated treatments would be necessary. The researchers also noted that combining this approach with other interventions might be even more effective.

While much work remains to be done before this approach can be applied to humans, the findings point toward a promising new strategy for combating diseases that have long been linked to aging and toxic protein buildup in the brain. Kelley said the long-term goal is to "help prevent or alleviate diseases like Alzheimer's and Parkinson's by improving brain waste clearance."

The study, "Restoration of cervical lymphatic vessel function in aging rescues cerebrospinal fluid drainage," was authored by Ting Du, Aditya Raghunandan, Humberto Mestre, Virginia Plá, Guojun Liu, Antonio Ladrón-de-Guevara, Evan Newbold, Paul Tobin, Daniel Gahn-Martinez, Saurav Pattanayak, Qinwen Huang, Weiguo Peng, Maiken Nedergaard, and Douglas H. Kelley.

Age, sex, and day/night cycle modulate the brain

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Source: CNRS INSIS

Using functional MRI to study the brains of male and female mice, a team from the Center for Biological and Medical Magnetic Resonance has highlighted the impact of sex, age, and lighting conditions on the resting-state connections between different brain areas involved in functions such as memory consolidation and processing visual or auditory data. The findings are published in the journal *NeuroImage*.

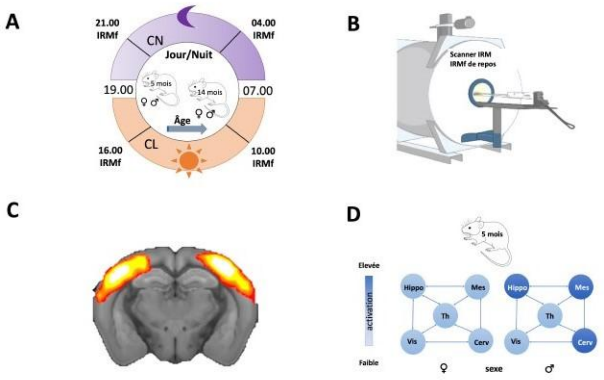
In a resting state, meaning in the absence of external stimuli or tasks performed by the individual, certain groups of neurons exhibit synchronous activity resulting from connections with other brain areas. Mapping these different connections constitutes

functional networks known as "resting-state" and forms the functional connectome.

These networks, which are involved in functions such as memory consolidation or processing visual or auditory data, evolve throughout life and can be altered by neurological diseases. These factors should therefore be considered for the correct interpretation of functional MRI (fMRI) images, especially when establishing treatment for patients with neurological diseases or who have suffered a stroke.

A team from the Center for Biological and Medical Magnetic Resonance (CRMBM, CNRS/Aix-Marseille University), in collaboration with the Institute of Systems Neuroscience (INS, Aix-Marseille University/Inserm), conducted a pilot study revealing the impact of sex, age, and the day/night cycle on the resting-state brain connectivity of mice observed by fMRI.

The fMRI, sensitive to local variations in blood flow and oxygenation induced by neuron activation, highlights the networks of neurons activated simultaneously in the resting state. Adult male and female mice, aged 5 and 14 months, were examined in resting-state fMRI at four moments of the day/night cycle (10:00 AM, 4:00 PM, 9:00 PM, 4:00 AM).



(A-B) fMRI study of the effects of the day/night cycle, sex, and age on the resting-state functional connectome of the mouse. Mice were studied at 2 different ages (5 and 14 months) and at 4 moments of the day/night cycle (10:00 AM, 4:00 PM, 9:00 PM, 4:00 AM) on an MRI scanner.

(C) The sensorimotor network involved in sensory perception and motor activity is one of the known functional networks identified in CRMBM's study.

(D) Example showing the effect of sex on one of the new networks identified by CRMBM: increased brain activity in memory-related structures in males compared to females at 5 months old, regardless of lighting conditions. CL = light condition, CN = night condition, Hippo = hippocampus, Mes = midbrain, Th = thalamus, Vis = visual cortex, Cerv = cerebellum.

The results revealed 16 resting-state functional networks, including 5 new ones, and

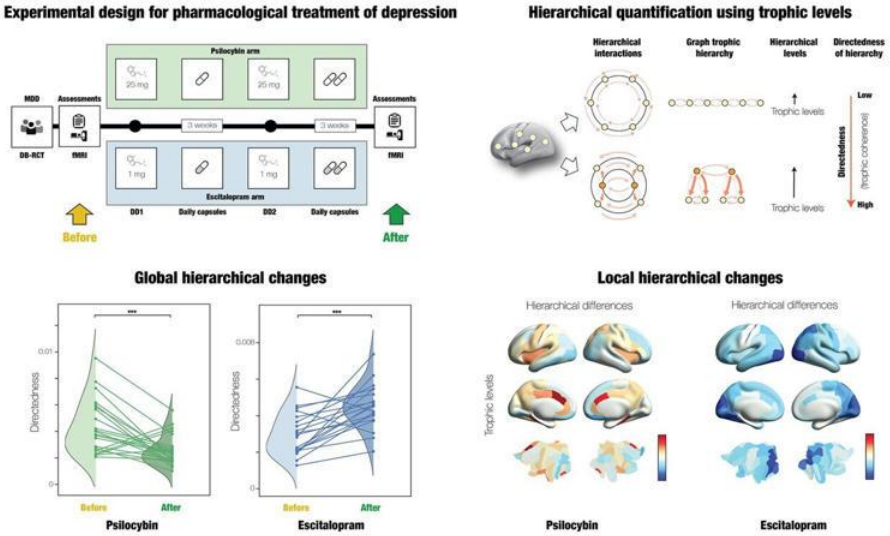
demonstrate the influence of the studied variables on the functional connectome of mice. Thus, fMRI images showed that the activity of a network involved in memorization was stronger in male mice than in female mice (all 5 months old), regardless of light conditions.

Furthermore, in 14-month-old female mice (the experiment could not be conducted with males), a significant increase in pineal gland activity was observed during periods of darkness. The pineal gland controls the production of melatonin, a hormone that plays a central role in regulating biological rhythms.

This initial study demonstrates the necessity to consider parameters such as age, sex, and the day/night cycle when interpreting resting-state fMRI images in mice used in research as models to study alterations in the functional connectome in diseases such as epilepsy or Alzheimer's disease.

References:

Impact of the day/night cycle on functional connectome in ageing male and female mice. Houéfa Armelle Lokossou, Giovanni Rabuffo, Monique Bernard, Christophe Bernard, Angèle Viola, Teodora-Adriana Perles-Barbacaru. *NeuroImage*, 15 April 2024, 120576. https://doi.org/10.1016/j.neuroimage.2024.120576
Article available on the open archive platform HAL



A cartoon of the pipeline and sketch of the results. Credit: Deco et al.

Depression is one of the most common mental disorders, affecting an estimated 300 million people worldwide. While there are currently numerous

pharmacological treatments for depression, how different treatments impact the brains of the patients they are administered to is not yet fully understood.

Selective serotonin re-uptake inhibitors (SSRIs) are among the most well-established antidepressant drugs worldwide. SSRIs can increase the activity of the neurotransmitter serotonin, which plays a key role in the regulation of sleep, mood, appetite and learning.

A more recently explored treatment option for depression is the naturally occurring psychedelic compound psilocybin, which is found in so-called "magic mushrooms." This compound has also been found to interact with serotonin receptors in the brain, which can improve the mood of individuals after consuming it.

Researchers at Universitat Pompeu Fabra, University of Oxford and other institutes across Europe recently carried out a study investigating the effects of these two different types of treatments on the brains of individuals diagnosed with depression, particularly on the brain's hierarchical organization following the intake of the drugs. Their paper, published in *Nature Mental Health*, suggests that these two treatment options result in very different hierarchical brain reconfigurations.

"We have long been interested in the orchestration of brain hierarchy in many different brain states and have been able to demonstrate in many papers that the human brain is hierarchically organized, orchestrating the global dynamics in order to perform effectively distributed computation," Gustavo Deco and Morten L. Kringelbach, co-authors of the paper, told Medical Xpress.

"We were interested in how hierarchy changes in treatment-resistant depression. Thanks to a recent randomized control trial, we were able to investigate two different pharmacological treatments."

As part of their recent paper, the researchers compared the effects of psilocybin to those of escitalopram, which is among the commonly prescribed SSRI drugs. All the study participants received two doses of psilocybin three weeks apart. For a period of six weeks, one group of participants also received a daily dose of escitalopram, while the other was administered a placebo (i.e., a neutral substance with no psychoactive effects).

"Our key idea was to study reconfiguration of the hierarchical organization of the brain in depression after different pharmacological treatment," said Deco and Kringelbach. "The experimental data was obtained from a two-armed double-blind phase II randomized controlled trial comparing psilocybin therapy (22 patients) with escitalopram (20 patients) from co-author Prof Carhart-Harris."

The researchers recorded the clinical outcomes of the two treatment plans followed by participants. They also collected scans of the patients' brains using functional magnetic resonance imaging (fMRI), both at the beginning of the study and after the patients had completed the 6-week treatment period.

"We used advanced whole-brain modeling, which fits a personalized computer model to the patient's empirical functional brain scans," explained Deco and Kringelbach. "We designed a framework to assess hierarchical reconfiguration by the global level of directedness of the generative effective connectivity (GEC) matrix underlying the whole-brain model. The GEC reflects the underlying anatomical structure and the dynamical functional activity in an asymmetric matrix which captures the hierarchical organization."

Using machine learning algorithms, Deco, Kringelbach and their colleagues were able to extract hierarchical features of the brain from the scans they collected. To frame their findings, they used a theoretical construct known as the "trophic coherence" framework, which in ecology describes the hierarchical food chain (i.e., carnivores eating herbivores, who in turn eat plants).

"According to this framework, a flat hierarchy is characterized by equal trophic levels and low directedness, which reflects low asymmetry in a network," said Deco and Kringelbach. "In contrast, a strong hierarchy is associated with high directedness and strong asymmetric connections in a many-layered network."

The researchers found that the hierarchical organization of brain dynamics is a highly precise measure of change following treatments. As part of their study, they used the trophic coherence framework to determine how the two treatments they assessed had reorganized the brain dynamics of the patients who received them.

"This approach allowed us to gather insights into the underlying mechanisms of depression and may in time lead to even better interventions," said Deco and Kringelbach. "Our results also confirm the hypothesis that problems with the

main regions of the global workspace orchestrating brain dynamics could be the main cause of neuropsychiatric disorders. Future larger studies should further investigate this hypothesis focusing on different neuropsychiatric diseases."

Essentially, the findings gathered by these researchers suggest that while both psilocybin and escitalopram can be effective treatments for depression, these two compounds resulted in significantly different brain hierarchy reconfigurations. Using machine learning-based computational models, the team was also able to predict patients' responses to treatment with an impressive accuracy of 85%.

Collectively, this study shows that SSRIs and psilocybin rebalance brain dynamics in completely different ways. In the future, the insight it gathered could inform pharmacological and psychiatric studies, contributing to the improvement of therapeutic interventions for depression.

"We now plan to use this novel framework to understand the orchestration of brain hierarchy in any brain state, since this would allow us to find novel ways to rebalance the brain in disease," added Deco and Kringelbach.

"The present whole-brain modeling framework could be used for treatment studies using any kind of effective intervention, whether pharmacological, electrical or behavioral. We also plan to use this methodology to study hierarchical reconfiguration in cognitive/behavioral tasks, and different brain states in healthy participants."

More information: Gustavo Deco et al, Different hierarchical reconfigurations in the brain by psilocybin and escitalopram for depression, *Nature Mental Health* (2024). DOI: 10.1038/s44220-024-00298-y.

Credit: Pixabay/CC0 Public Domain

Thyroid hormone plays a key role in regulating a range of physiologic functions, including metabolism, temperature, heart rate, and growth. It accomplishes this impressive array of activities by interacting with almost every

organ system in the body. Yet despite a long history of research on how thyroid hormone influences different organs, its effects on arguably the most crucial organ—the brain—have remained shrouded in mystery.

Now, scientists at Harvard Medical School have gained new insights into thyroid hormone's effects on the brain. The work, conducted in mice and published Aug. 22 in *Cell*, shows that thyroid hormone changes the wiring of brain circuits in a manner that drives animals to engage in exploratory behavior.

By simultaneously changing brain wiring and altering metabolic rate, the researchers concluded that thyroid hormone coordinates the brain and body to produce exploratory behavior when it is most needed—for example, during seasons when animals need to find mates or stockpile resources.

"It's well known that thyroid hormone modulates metabolism, and now we've shown that it also modulates exploratory behaviors through direct action on the brain," said lead author Daniel Hochbaum, research fellow in neurobiology in the Blavatnik Institute at HMS.

The findings also help elucidate how low levels of the hormone could lead to depressive states marked by a low desire to explore, while too much could precipitate manic states characterized by an extreme desire for exploration. Thus, the researchers see their work as an important step toward understanding how aberrant levels of thyroid hormone could contribute to certain psychiatric conditions.

Propelled by a personal purpose

Hochbaum's interest in thyroid hormone is a personal one: His wife was diagnosed with hyperthyroidism after experiencing profound and sudden behavioral and metabolic changes. Her symptoms resolved with treatment, but Hochbaum wanted to know more about the hormone's effects on the brain.

"I was really surprised to see that thyroid hormone had large psychiatric effects," Hochbaum said.

He learned that too little thyroid hormone slows down metabolism and can result in symptoms of depression, while too much speeds up metabolism and can lead to symptoms of mania. Yet he couldn't find a satisfactory scientific explanation for how this happens.

During a serendipitous conversation with Bernardo Sabatini, the Alice and Rodman W. Moorhead III Professor of Neurobiology at HMS, Hochbaum found that Sabatini shared his interest in the topic.

"Why thyroid hormone changes behavior has been something that's puzzled me ever since medical school," said Sabatini, who is also director of the Kempner Institute for the Study of Natural and Artificial Intelligence at Harvard University and senior author on the new study. "It was not clear why this hormone should even enter the brain at all."

And with that, a project to explore thyroid hormone's function in the brain was born.

Linking brain, body, and behavior

Thyroid hormone circulates in the bloodstream, traveling to almost every cell and tissue in the body. Its levels are controlled by a complex set of interactions between three players: the thyroid gland, the pituitary gland at the base of the brain, and the hypothalamus, a brain structure located just above the pituitary gland.

However, the receptor for thyroid hormone is expressed by cells throughout the entire brain, including in areas of the cortex responsible for high-level cognition like planning and decision-making.

"What is quite remarkable is that in the adult brain, the thyroid hormone receptor is not only in the hypothalamus, but it's basically everywhere," Hochbaum said.

To investigate why, Hochbaum, Sabatini, and their team performed genetic sequencing on individual cortical cells in mice. They found that the hormone acts on neuronal circuits in the cortex by turning on various genes, essentially changing the wiring of brain cells.

Moreover, when researchers induced higher levels of thyroid hormone in the cortex, mice became more willing to explore the environment and take risks.

Conversely, when researchers blocked the hormone's action in only the cortex, the animals no longer changed how much they explored based on thyroid hormone levels.

"This told us that thyroid hormone is doing important things directly in the cortex," Hochbaum said.

Yet the findings raised a new question: Why would it be beneficial for a hormone that controls metabolism to also alter brain circuits that affect behavior?

To address this question, the researchers turned to previously published field studies that observed behavior in the wild and measured thyroid hormone of lemurs, squirrel monkeys, and other mammals. The research revealed that hormone levels, and in turn metabolic rates, tended to be higher in warmer seasons when food and resources were more abundant—and animals explored more during those seasons.

The studies, combined with the new findings, Hochbaum said, provide an essential missing link between thyroid hormone's effects on the brain and body.

"We think that thyroid hormone acts directly on brain circuits to coordinate exploratory behaviors with metabolic rate," he added. "It's syncing up your brain and body for the current environment."

Or, as Sabatini put it, "It seems like thyroid hormone prompts the body to tell the brain to go explore and capture resources."

Looking ahead

The way in which thyroid hormone regulates physiology is highly conserved between humans and other mammals, the researchers said, so they suspect that a similar brain-body connection exists in humans.

In fact, a 2024 study led by the same researchers linked higher thyroid hormone levels in U.S. adults to greater employment levels and more hours worked.

The researchers are now exploring this connection in people in Indonesia who experienced the 2004 tsunami. They are interested in whether psychological trauma from the natural disaster has led to long-term changes in thyroid hormone levels.

The team also wants to investigate the basic biology of the exploratory brain circuits that are activated by increased thyroid hormone. The researchers hope that their work could highlight brain circuits relevant to psychiatric conditions such as depression and bipolar disorder.

"The thought is that these conditions are also shaping exploratory activity, so perhaps manipulating thyroid hormone to change brain circuits will reveal relevant points of entry for treatment," Hochbaum said.

More information: Daniel Hochbaum et al, Thyroid hormone remodels cortex to coordinate body-wide metabolism and exploration, *Cell* (2024). DOI: 10.1016/j.cell.2024.07.041. www.cell.com/cell/fulltext/S0092-8674(24)00835-3

Provided by Harvard Medical School

Tinnitus, often characterized by the persistent ringing or hissing in the ears, has plagued the lives of approximately 750 million individuals worldwide. While it is not a disease in itself, this debilitating condition has long eluded a definitive cure or standard treatment, leaving countless sufferers in search of relief.

However, a recent study conducted by Brazilian scientists affiliated with the Optics and Photonics Research Center (CEPOF) may offer newfound hope to tinnitus patients. Their research, which rigorously compared various existing treatments, suggests that low-level laser therapy, coupled with photobiomodulation, is emerging as the most effective solution to date.

This groundbreaking study, reported in the Journal of Personalized Medicine, provides promising insights into the future management of tinnitus.

Tinnitus: A Global Challenge

Tinnitus is a prevalent symptom experienced by millions worldwide, impacting their quality of life. A European study analyzing patient data spanning five decades revealed the staggering scope of this issue.

Brazilian researchers compared the therapies used most frequently for tinnitus, which affects some 750 million worldwide. (CREDIT: Panhóca, V.H. et al./J. Pers. Med.)© The Brighter Side of News

From a buildup of earwax and inadequate inner ear circulation to more severe factors such as brain damage and bruxism, the causes of tinnitus are diverse. Yet, despite its prevalence and impact, there are no standard treatments or FDA-approved drugs available to address this ailment.

Dr. Vitor Hugo Panhóca, a researcher at CEPOF, emphasized the need for effective tinnitus treatments, stating, "Tinnitus is a very widespread symptom throughout the general population. It's treated with a vast number of methods, from ear lavage to local anesthetics, anti-depressants, anti-histamines, anti-psychotics, and sedatives, with different results." This lack of consensus underscores the urgency of finding viable treatment options.

The Quest for Effective Treatments

In response to the challenges posed by tinnitus, Dr. Panhóca and his team embarked on a rigorous research endeavor. Over the course of four weeks, they investigated alternative and complementary therapies for idiopathic and refractory tinnitus in more than 100 individuals, aged 18 to 65, randomly divided into ten groups.

These therapies included laser acupuncture, flunarizine dihydrochloride, Ginkgo biloba, and low-level laser stimulation of the internal auditory canal (transmeatal stimulation), both alone and in combination with various adjunct therapies.

Each patient underwent eight bi-weekly treatment sessions and was assessed using a "tinnitus handicap inventory questionnaire" featuring 25 questions. This questionnaire included a functional subscale with 11 questions addressing mental, social, occupational, and physical limitations due to tinnitus.

Upon analyzing the data, the researchers made several noteworthy discoveries. The most promising results were observed in patients treated with laser acupuncture alone and transmeatal low-power laser stimulation alone.

Notably, the latter group exhibited even greater improvement when the duration of laser irradiation was extended from 6 to 15 minutes. Additionally, combinations of laser therapy with vacuum therapy or Ginkgo biloba, as well as

laser acupuncture alone and flunarizine dihydrochloride alone, also demonstrated lasting therapeutic effects.

Barplot comparing the non-normalized TH1 scores at T0, T1 and T2 between tinnitus treatment modalities explored in this study (from G1 to G10). (CREDIT: Journal of Personalized Medicine)© The Brighter Side of News

Dr. Panhóca explained, "The positive effects include anti-inflammatory action and relaxation. We believe laser therapy can increase peripheral irrigation, which may be the main cause of the problem in many cases, as well as stimulating inner ear cell proliferation and collagen production." These findings suggest that low-level laser therapy may address underlying factors contributing to tinnitus.

Standardizing Treatment Protocols

While the efficacy of laser therapy in alleviating tinnitus is not entirely novel, the CEPOF study makes significant strides towards standardizing treatment protocols. This development holds great promise for healthcare professionals, including dentists, ear, nose, and throat specialists, and speech therapists, who treat tinnitus patients.

Currently, the literature lacks consensus on the optimal number of sessions and treatment intensity, making it challenging to provide consistent care.

Comparison between study groups showing the evolution of different interventions to treat tinnitus. (CREDIT: Journal of Personalized Medicine)© The Brighter Side of News

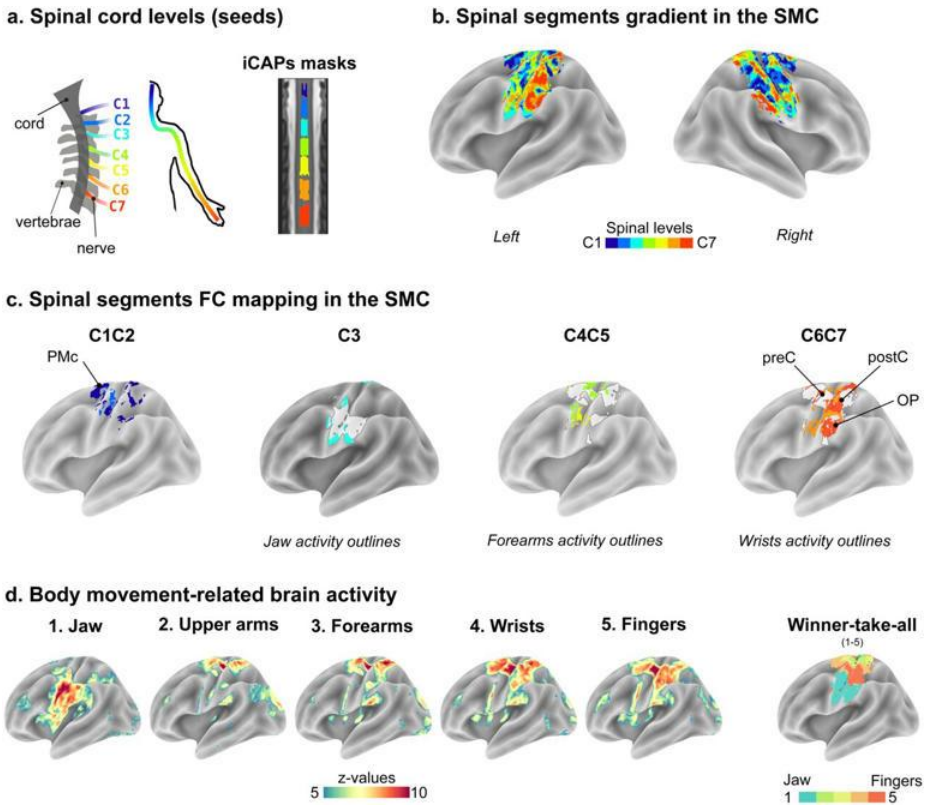
Dr. Panhóca emphasized the importance of understanding successful therapies to streamline future treatments, saying, "Understanding how successful therapies work will help us focus on the most productive approaches in forthcoming studies. This is part of the learning curve when you innovate in health treatments like this." Additionally, long-term effects of laser therapy must be thoroughly investigated to ensure its safety and efficacy.

This pioneering study received support from FAPESP, which awarded a postdoctoral scholarship to Dr. Fernanda Rossi Paolillo, a key contributor to the research.

The study was conducted in collaboration with researchers at Irmandade Santa Casa de Misericórdia Hospital in São Carlos, University of Central São Paulo

(UNICEP), and the Integrated Therapy Center in Londrina, Brazil. Furthermore, international collaboration with the Tyndall National Institute at University College Cork (UCC) in Ireland enriched the study's scope.

While further research is necessary to confirm the long-term efficacy and safety of laser therapy, these findings represent a significant step forward in the quest to alleviate the burden of tinnitus on those affected by it.



Gradient of cervical spinal cord functional connectivity along the SMC network. Credit: Imaging Neuroscience (2024). DOI: 10.1162/imag_a_00284

The brain and spinal cord are the central pillars of the human central nervous system (CNS), orchestrating everything from movement to sensation. Despite significant advances in neuroscience, our understanding of how these two crucial components of the CNS interact remains limited.

A comprehensive view of the entire CNS will bolster the development of therapies for neurological disorders, particularly those involving both the brain and spinal cord, such as spinal cord injuries and neurodegenerative diseases.

Bridging this critical knowledge gap, researchers at EPFL's Neuro X Institute, UNIGE's Department of Radiology and Medical Informatics, and McGill University's Montreal Neurological Institute (The Neuro) have developed a tool to significantly advance our understanding of the CNS organization.

Their new study, published in *Imaging Neuroscience*, successfully maps the functional connectivity between the brain and spinal cord in humans, providing a more detailed view of how these two critical components interact.

"This research allows us to see the CNS as a whole, which is crucial if we want to develop effective therapies that target complex neurological conditions. The imaging tool—a set of technologies and protocols—greatly improves our understanding of somatotopic organization.

"This means that we can now see how different parts of the body are mapped onto specific areas of the brain and spinal cord," says Dimitri Van De Ville, head of EPFL's Medical Image Processing Laboratory (MIP:lab) and one of the lead authors of the study.

The CNS network down to the smallest detail

This breakthrough, achieved through a detailed analysis of simultaneous brain and cervical spinal cord functional magnetic resonance imaging (fMRI) data, provides unprecedented insights into how the brain and spinal cord work together to represent the body as a whole. What emerges is a body map that extends across the different levels of the CNS.

Building on prior research in functional imaging techniques developed at the MIP:Lab, researchers used algorithmic models to isolate and identify specific regions of interest in both the brain and spinal cord. For the spinal cord, this approach allowed accurate delineation of the spinal segments responsible for innervating different body parts, enhancing our understanding of the organization within the spinal cord itself.

To explore how the brain and spinal cord interact, the researchers employed functional connectivity analyses. By examining synchronized activity between the brain and spinal cord, they were able to uncover how specific areas in the brain and spinal cord correspond to different parts of the body. This approach provided a detailed map of the networks that connect the brain and spinal cord, offering new insights into how the central nervous system operates as a unified whole.

A methodological framework for future progress

"Our findings show that even at rest, the brain and spinal cord maintain a precise map of the body," says Nawal Kinany, co-first author of the paper. "The methodological framework introduced in this study can also be deployed in clinical populations, for instance to investigate CNS reorganization after lesions or limb amputation. In the future, this knowledge could contribute to the development of more accurate treatments and interventions, ultimately improving patient outcomes."

Another key innovation lies in the researchers' ability to overcome the technical challenges of imaging two anatomically distinct parts of the central nervous system at the same time, which traditionally require separate scans.

The data for the study were collected at the The Neuro in Montreal, under the supervision of Julien Doyon, a leading researcher in the field and a key collaborator on the project. His expertise in neuroimaging and the lab's state-of-the-art facilities were crucial in capturing the high-quality fMRI data that made this detailed mapping of brain-spinal cord connectivity possible.

By integrating cutting-edge imaging techniques and collaborative research, the findings provide a foundational framework for future explorations into CNS function and dysfunction.

More information: Caroline Landelle et al, Cerebro-spinal somatotopic organization uncovered through functional connectivity mapping, *Imaging Neuroscience* (2024). DOI: 10.1162/imag_a_00284

Provided by Ecole Polytechnique Federale de Lausanne

New research provides insight into how exercise strengthens brain connections© PsyPost

A new study sheds light on how exercise boosts brain function by exploring the role of nerves in muscle-brain communication. The study, published in the *Proceedings of the National Academy of Sciences*, reveals that muscles release molecules that support brain cell communication and development, and this release is driven in part by signals from the nerves that tell muscles to move. These findings help clarify the complex relationship between exercise, muscle function, and brain health.

Previous research has established that when muscles are engaged during physical activity, they release molecules that travel through the bloodstream and positively affect brain cells. These molecules, such as hormones and small vesicles containing RNA, help brain cells form stronger connections and communicate more efficiently.

However, the role of the nerves that trigger muscle movement in this process was not well understood. With age, or due to injury and disease, people tend to lose nerve connections to their muscles. This decline in nerve supply can lead to muscle breakdown and contribute to broader organ dysfunction, including in the brain.

The researchers aimed to investigate how nerve signals to muscles influence the release of molecules that support brain function. They hoped to better understand the mechanisms of this muscle-brain communication and identify

ways to preserve or enhance this connection, particularly for older adults or those with neuromuscular diseases. If successful, their findings could provide a foundation for developing treatments that target muscle-brain interactions, potentially helping people maintain cognitive function even as they lose muscle mass and nerve connections.

To explore the role of nerve signals in muscle-brain communication, the researchers created two different models of muscle tissue: one that included nerve cells, and one that did not. This allowed them to compare the two and determine how the presence of nerves affected the muscle's ability to release brain-enhancing molecules.

The muscles were placed in a laboratory dish, where one group of tissues received nerve cells, allowing the muscle and nerve cells to form connections similar to what happens in the body. These nerve-muscle connections are known as neuromuscular junctions. The second group of muscle tissues was left without any nerve cells. After establishing these two groups, the researchers stimulated the nerve-connected muscles using glutamate, a neurotransmitter that carries signals in the brain and nervous system, to mimic the kind of stimulation muscles would receive during exercise.

The researchers then measured the amount and types of molecules released by the muscles into the surrounding fluid. They specifically looked at two types of molecules: hormones, like irisin, which are known to have beneficial effects on the brain, and extracellular vesicles, tiny particles that carry RNA and other molecular cargo between cells.

In addition to measuring the overall quantity of molecules, the team also examined the specific types of RNA found within the vesicles, as these RNA fragments can influence brain cell development and communication.

The study revealed several key findings. First, the muscle tissues connected to nerves released significantly more brain-beneficial molecules compared to muscles without nerves. Specifically, the nerve-connected muscles produced higher levels of the hormone irisin, which has been linked to the positive effects of exercise on brain health. Irisin has been shown to support brain function by crossing the blood-brain barrier and promoting neurogenesis, the process by which new brain cells are formed.

Furthermore, the nerve-connected muscles also released a greater variety of extracellular vesicles, which carried RNA fragments associated with brain development and neuron communication. These vesicles are particularly important because they can transport molecular signals that help brain cells form stronger connections and communicate more effectively.

When the researchers stimulated the nerve-connected muscles with glutamate, they saw an even larger increase in the release of irisin and extracellular vesicles. The RNA fragments found in the vesicles were more diverse in this stimulated group, suggesting that the nerve signals to muscles not only increase the quantity of molecules released but also enhance the complexity of the molecular cargo, making it more beneficial for brain function.

These findings highlight the crucial role that nerve signals play in promoting muscle-brain communication. As muscles lose their nerve connections with age or due to injury, their ability to release these brain-supporting molecules diminishes, potentially contributing to cognitive decline and other brain-related issues.

Although this study provided new insights into the role of nerves in muscle-brain communication, it had some limitations. First, the experiments were conducted using lab-grown muscle tissues, which, while helpful for isolating certain factors, do not fully replicate the complex environment of a living organism. Future studies will need to test whether these findings hold true in living animals and eventually in humans.

Moving forward, the researchers plan to investigate the precise mechanisms at the junction between nerves and muscle cells. They hope to determine whether nerve impulses directly affect the production of brain-boosting factors or primarily regulate their release. This knowledge could help inform the development of targeted therapies for people with neuromuscular diseases or age-related muscle loss.

The team also aims to use their laboratory muscle models as platforms for efficiently producing brain-beneficial molecules. By simulating exercise in a lab setting, they hope to better understand how to enhance the release of these molecules, potentially paving the way for new treatments that mimic the benefits of exercise for people who are unable to engage in physical activity due to injury or disease.

The study, "Neuronal innervation regulates the secretion of neurotrophic myokines and exosomes from skeletal muscle," was authored by Kai-Yu Huang, Gaurav Upadhyay, Yujin Ahn, Masayoshoi Sakakura, Gelson J. Pagan-Diaz, Younghak Cho, Amanda C. Weiss, Chen Huang, Jennifer W. Mitchell, Jiahui Li, Yanqi Tan, Yu-Heng Deng, Austin Ellis-Mohr, Zhi Dou, Xiaotain Zhang, Sehong Kang, Qian Chen, Jonathan V. Sweedler, Sung Gap Im, Rashid Bashir, Hee Jung Chung, Gabriel Popescu, Martha U. Gillette, Mattia Gazzola, and Hyunjoon Kong.

Can we change how our brains age? These scientists think it's possible© Getty Images

It's long been known that our lifestyles can help to keep us healthier for longer. Now scientists are asking whether new technology can also help slow down the ageing process of our brains by keeping track of what happens to them as we get older.

One sunny morning, 76-year-old Dutch-born Marijke and her husband Tom welcomed me in for breakfast at their home in Loma Linda, an hour east of Los Angeles.

Oatmeal, chai seeds, berries, but no processed sugary cereal or coffee were served - a breakfast as pure as Loma Linda's mission.

Loma Linda has been identified as one of the world's so-called Blue Zones, places where people have lengthier-than-average lifespans. In this case, it is the city's Seventh-Day Adventist Church community who are living longer.

They generally don't drink alcohol or caffeine, stick to a vegetarian or even vegan diet and consider it a duty of their religion to look after their bodies as best they can.

This is their "health message", as they call it, and it has put them on the map - the city has been the subject of decades of research into why its residents live better for longer.

Dr Gary Fraser from the University of Loma Linda told me members of the Seventh-Day Adventist community there can expect not only a longer lifespan, but an increased "healthspan" - that is, time spent in good health - of four to five years extra for women and seven years extra for men.

Marijke and Tom had moved to the city later in life, but both were now firmly embedded in the community.

There's no great secret to Loma Linda. Its citizens are simply living a really healthy life, keeping mentally stimulated and valuing the community a religion can often provide.

There are regular lectures on healthy living, musical get-togethers and exercise classes.

I chatted to Judy, who lives with 112 others at an assisted living facility where there was always the "ability to have heart-opening, brain-opening conversations", she told me.

"What I didn't realise was how important socialisation is to your brain... without it, it seems to shrink and go away," Judy said.

Science has long recognised the benefits of social interactions and avoiding loneliness.

But now it's also possible to identify whose brains are ageing faster than they should, so they can be tracked and in future potentially be treated better preventatively.

As we move towards more personalised, predictive, preventative healthcare models, early diagnosis will be crucial in all areas of health - powered by the incredible possibilities of AI and big data.

He had created them using MRI scans, data from 15,000 brains and the power of artificial intelligence to understand the trajectory of both brains that are ageing healthily and those in which there is a disease process, such as dementia.

"It's a very sophisticated way to look at patterns that we don't necessarily know about as humans, but the AI algorithm is able to pick up on them," he said.

Prof Irimia did, of course, take a look inside my head.

I'd had a functional MRI scan ahead of my visit and, after analysing its results, Prof Irimia told me I had a brain age eight months older than my chronological

age (although apparently the bit that controls talking wasn't ageing so much. I could have told him that). However, Prof Irimia suggested that the results fall within a two-year error margin.

Private companies are starting to commercialise this technology, too. One firm, Brainkey, is offering the service in a variety of clinics around the world. Its founder Owen Philips told me that in future, getting an MRI should become easier.

"It's becoming much more accessible for people to get an MRI scan, and the images coming off them are getting even better and better," he said.

"I don't mean to nerd out there. But the technology is just getting to a point where we are able to see things much earlier than we could in the past. And that means we can understand exactly what's happening in an individual patient's brain. With AI, we can support that."

In contrast to what Prof Irimia's analysis of my MRI scan had told me, Brainkey's estimate knocked a year off my brain's biological age. I was also presented with a 3D-printed model of it, which appeared substantial and, I was assured, was life-sized.

Lara Lewington with the life-sized 3D-printed model of her own brain© BBC

The aim here is not just a more precise approach to treatment, but also to be able to quantify how well any interventions are working.

Dramatic increases in life expectancy over the past 200 years have given rise to a host of age-related diseases. I did wonder whether, if we all lived long enough, dementia might come knocking at all our doors.

Prof Irimia said this was a theory many have investigated albeit not proven, adding that the aim was to find a way to keep on pushing dementia back, hopefully beyond our life expectancies.

And all of this takes us back to the same point. Every scientist and doctor, as well as those Blue Zoners, say lifestyle is key. Good diet, keeping active, mentally stimulated and happy are crucial to how our brains age.

There's another important factor too, according to Matthew Walker, professor of neuroscience and psychology at the University of California, Berkeley, and author of the best-selling book Why We Sleep.

"Sleep is the single most effective thing you can do every day to reset your brain and body health," he evangelised. "There is no operation of your mind that is not wonderfully enhanced when you get sleep, or demonstrably impaired when you don't get enough."

He spoke of our brains' cleansing system, which functions during our slumber by washing away the beta-amyloid and tau proteins - these are "two of the main culprits underlying Alzheimer's".

Changes in sleep patterns are also associated with dementia. Prof Walker described how we don't just see this in our 60s or 70s - it can begin during our 30s. So, identifying those changes through sleep tracking could potentially become a "model of midlife prevention".

Fauna Bio, a biotech company on the outskirts of San Francisco, is collecting data on ground squirrels during and after hibernation. In this state of torpor, as it is known, the squirrels' body temperature drops and their metabolic rate is reduced to just 1% of normal.

During this time, they appear to be able to regrow neurons and remake the connections their brains had lost. The company's aim is to try and create drugs to replicate this process in humans, without them needing to spend half the year underground. Even if some may long for that.

Untreated depression has also been shown to raise our risk of dementia. Professor Leanne Williams of Stanford University has identified a method of "visualising" some forms of depression on the brain using an MRI scan, and thus seeing if treatment has worked.

This may be able to help scientists understand more abotu the root causes of mental health conditions such as depression, as well as providing a way to quantify how treatment is going for a patient.

Few have put more faith in science to achieve longevity than Bryan Johnson - the tech entrepreneur spending millions in an effort to reverse his biological age.

Dozens of supplements, 19 hours a day of fasting, workouts that make him look as though he's going to burst and an array of (sometimes controversial) treatments are what he hopes will turn back the clock.

Leg exercise is critical to brain and nervous system health© Organically Human

Groundbreaking research shows that neurological health depends as much on signals sent by the body's large, leg muscles to the brain as it does on directives from the brain to the muscles. Published today in *Frontiers in Neuroscience*, the study fundamentally alters brain and nervous system medicine-giving doctors new clues as to why patients with motor neuron disease, multiple sclerosis, spinal muscular atrophy and other neurological diseases often rapidly decline when their movement becomes limited.

"Our study supports the notion that people who are unable to do load-bearing exercises-such as patients who are bed-ridden, or even astronauts on extended travel-not only lose muscle mass, but their body chemistry is altered at the cellular level and even their nervous system is adversely impacted," says Dr. Raffaella Adami from the Università degli Studi di Milano, Italy.

The study involved restricting mice from using their hind legs, but not their front legs, over a period of 28 days. The mice continued to eat and groom normally and did not exhibit stress. At the end of the trial, the researchers examined an area of the brain called the sub-ventricular zone, which in many mammals has the role of maintaining nerve cell health. It is also the area where neural stem cells produce new neurons.

Limiting physical activity decreased the number of neural stem cells by 70 percent compared to a control group of mice, which were allowed to roam. Furthermore, both neurons and oligodendrocytes-specialized cells that support and insulate nerve cells-didn't fully mature when exercise was severely reduced.

The research shows that using the legs, particularly in weight-bearing exercise, sends signals to the brain that are vital for the production of healthy neural cells, essential for the brain and nervous system. Cutting back on exercise makes it

difficult for the body to produce new nerve cells-some of the very building blocks that allow us to handle stress and adapt to challenge in our lives.

“It is no accident that we are meant to be active: to walk, run, crouch to sit, and use our leg muscles to lift things,” says Adami. “Neurological health is not a one-way street with the brain telling the muscles ‘lift,’ ‘walk,’ and so on.”

The researchers gained more insight by analyzing individual cells. They found that restricting exercise lowers the amount of oxygen in the body, which creates an anaerobic environment and alters metabolism. Reducing exercise also seems to impact two genes, one of which, CDK5Rap1, is very important for the health of mitochondria-the cellular powerhouse that releases energy the body can then use. This represents another feedback loop.

These results shed light on several important health issues, ranging from concerns about cardio-vascular impacts as a result of sedentary lifestyles to insight into devastating diseases, such as spinal muscular atrophy (SMA), multiple sclerosis, and motor neuron disease, among others.

“I have been interested in neurological diseases since 2004,” says co-author Dr. Daniele Bottai, also from the Università degli Studi di Milano. “The question I asked myself was: is the outcome of these diseases due exclusively to the lesions that form on the spinal cord in the case of spinal cord injury and genetic mutation in the case of SMA, or is the lower capacity for movement the critical factor that exacerbates the disease?”

This research demonstrates the critical role of movement and has a range of potential implications. For example, missions to send astronauts into space for months or even years should keep in mind that gravity and load-bearing exercise play an important role in maintaining human health, say the researchers.

“One could say our health is grounded on Earth in ways we are just beginning to understand,” concludes Bottai.

Written by: Frontiers.

Brain-Computer Interfaces©Image Credit: Kohji Asakawa from Pixabay

These devices let brains talk directly to computers. They could help paralyzed people move again or let us control machines with our thoughts. Some companies are already testing early versions. By 2030, they might be helping people with disabilities and changing how we all use technology.

Ever wish you could memorize every detail? Colleague's outfit? Neighborhood cat's meows? Newsflash: It's a memory meltdown waiting to happen!

Your brain, like a digital detoxing device, declutters by forgetting. Not a weakness, but a well-being weapon! Dive into the surprising science of remembering... less.

As Dubai-based neuropsychiatrist Nadia Khan explains, “Forgetting actually helps us focus on what matters now. We don’t carried away with every detail from the past. And so, with a little help from forgetting, we can actually adjust to different

situations with agility. You can also see it as prioritising tasks on your list; you deal with the relevant ones first," she says.

Neurological housekeeping

Research indicates that, at least in some cases, forgetting is due to "altered memory access" rather than memory loss. Image Credit: Shutterstock
As Khan explains, our brain is wired to optimise memory storage. It's not intended to carry every detail. This complex, dynamic process of forgetting actually allows us to rid ourselves of outdated information. It makes room for learning and experiences. This kind of neurological housekeeping enhances our ability to process the present better. "As a result, we make healthier decisions that actually benefit our well-being," she says.

Needless to say, forgetting usually comes at the cost of information, but research indicates that, at least in some cases, forgetting is due to "altered memory access" rather than memory loss.

So, how does this work? Well, it comes down to the neurons. The international journal, Nature Reviews Neuroscience, explained the complicated neuron activity that goes on, during the process of forgetting and recalling. In the study, the researchers examined the unique ensemble of neurons called "engram cells". When we recall a memory, these cells fire collectively, and our memory surges. However, what happens when we forget?

As the researchers explain, forgetting doesn't necessarily mean that the memory is gone. Instead, it proposes that these engram cells become inaccessible. However, this "inaccessibility", is actually an active process.

It's not a passive decay, as the researchers emphasise. In fact, our brain actively remodels the memory circuits, making specific engram cells harder to access based on the environmental factors. And so, in certain environments, it's not completely essential to hold on to every detail. When we forget, we actually focus on what's important.

The research highlights that while natural forgetting is generally a necessary process, it could potentially be reversed in certain situations. However, in the case

of severe diseases like Alzheimer's, the natural mechanisms are 'hijacked', leading to excessive forgetting and memory loss. These new findings could open up avenues for research into how to restore healthy forgetting processes and treat memory loss in diseases like Alzheimer's.

Forgetting: An active part of learning

In order to update your memory, your brain does a little clever forgetting. It provides more clarity to decision-making. Image Credit: Shutterstock
Forgetting could just be an ally in learning and mastery, if done right.

According to the 2023 study published in the US-based scientific journal Cell Reports titled Adaptive expression of engrams by retroactive interference, researchers studied how forgetting things is actually an active part of learning and memory maintenance. In fact, it is actually an active process that involves neural plasticity. This helps in modulating the functionality of specific memories.

In simpler words, in order to update your memory, your brain does a little clever forgetting. It provides more clarity to decision-making.

Forgetting is an important part of the learning process, says Dubai-based neuropsychiatrist, Anne Thomas. It helps the brain to sort, separate crucial information from all the details. In this day and age of excessive information overload, this particular filtering process is essential, says Khan. In order to retrieve information that is relevant and appropriate, we forget the unwanted and irrelevant information.

How to revive dormant memories

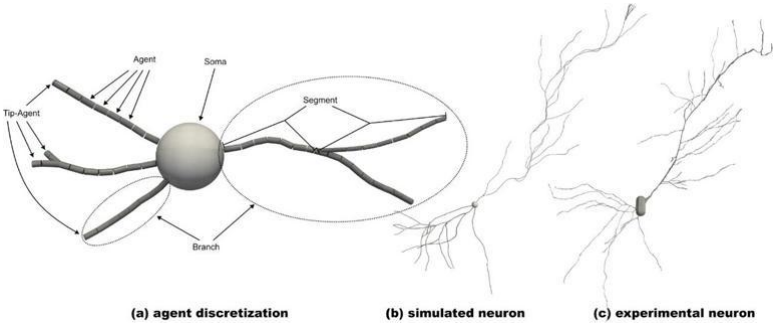
These forgotten memories still exist; they haven't been wiped out, as the Cell Reports study explains. They just become dormant. As Thomas explains with an example: For instance, you can't remember someone's name. Yet, when they re-introduce themselves, you realise that you knew it all along.

Your brain is playing a clever trick, there. "These forgotten memories aren't actually gone," explains Thomas, elaborating on the process of 'recognition' and 'recall'. So, when you see a familiar face, you recognise the familiarity, even if you're not able to recall the name. It's kind of like your brain getting a hint. You just take time to recall the name.

And so, in order to "revive" dormant memories, you need to review what you had previously learned, explains Thomas. For example, if you studied the previous night, and slept on time, the next morning, do a quick review of what you read. According to a 2016 study, titled Relearn Faster and Retain Longer published in US-based Academic journal Psychological Science, people who studied before bed, slept, and then later did review the next morning not only spent less time studying, they also increased their long-term retention memory by 50 percent. "A good rest does help your brain in filing away what you learned, and it also makes the information easier to access," explains Khan.

The brain needs to keep learning and adapting, she says. Learning and forgetting is a deeply inter-linked process. If you learn something, you need to keep reviewing it, to keep it in your memory. You need to keep revisiting it as well, so that the process of retrieval becomes easier.

This also helps you strengthen important memories through reviewing and tests, you make the important ones far more accessible, adds Khan. "Your brain needs to keep forging connections and building new pathways. 'Forgetting' old connections forces your brain to create new ones, keeping it flexible and adaptable," she says.



3D Mechanistic ABM for neuronal growth. Panel a shows the agent-based discretization and the early stage of a neuron simulation (pyramidal cell). The center is the spherical soma (cell body). The dendrites are discretized with small, cylindrical agents. Typically, the tips drive the growth (Shree et al. 2022); hence, we differentiate between the

general and tip agents. The agents define a tree-like structure with different segments and branches. b Pyramidal cell at the end of the simulation. c Experimental pyramidal cell in the mouse hippocampus observed by Benavides-Piccione et al. (2019) (NMO_147071). Credit: Journal of Mathematical Biology (2024). DOI: 10.1007/s00285-024-02144-2

A new computer simulation of how our brains develop and grow neurons has been built by scientists from the University of Surrey. Along with improving our understanding of how the brain works, researchers hope that the models will contribute to neurodegenerative disease research and, someday, stem cell research that helps regenerate brain tissue.

The research has been published in the *Journal of Mathematical Biology*.

The research team used a technique called Approximate Bayesian Computation (ABC), which helps fine-tune the model by comparing the simulation with real neuron growth. This process ensures that the artificial brain accurately reflects how neurons grow and form connections in real life.

The simulation was tested using neurons from the hippocampus—a critical region of the brain involved in memory retention. The team found that their system successfully mimicked the growth patterns of real hippocampal neurons, showing the potential of this technology to simulate brain development in fine detail.

Dr. Roman Bauer from the University of Surrey's School of Computer Science and Electronic Engineering said, "How our brain works is still one of the greatest mysteries in science. With this simulation, and the rapid advancements in artificial intelligence, we're getting closer to understanding how neurons grow and communicate. We hope that one day this work could lead to better treatments for devastating diseases like Alzheimer's or Parkinson's—changing lives for millions."

The accuracy of the model is closely tied to the quality of the data used to calibrate it. If the real-life neuron data is limited or incomplete, the precision of the simulation may decrease. While the current model has shown impressive results in replicating the growth of specific neurons, such as hippocampal pyramidal cells, further adjustments may be needed to accurately simulate other types of neurons or regions of the brain.

The computer simulation is built from the BioDynaMo software, which Dr. Bauer co-developed. The software supports scientists to easily create, run, and visualize multi-dimensional agent-based simulations, be they biological, sociological, ecological or financial.

More information: Tobias Duswald et al, Calibration of stochastic, agent-based neuron growth models with approximate Bayesian computation, *Journal of Mathematical Biology* (2024). DOI: 10.1007/s00285-024-02144-2

Provided by University of Surrey

Oligodendrocyte Precursor Cells, or OPCs (the purple and green blobs above), prune unneeded synapses (the silver streaks) in the brain's visual cortex in response to new information and experiences. Credit: Cheadle lab/Cold Spring Harbor Laboratory

Imagine yourself sometime in the far future aboard a routine rocket to Mars.

Someone just spilled their drink. Without gravity, it collects in floating blobs that ripple right before your eyes. Now freeze.

What you see might look something like the above image from Cold Spring Harbor Laboratory's (CSHL's) Cheadle lab. But those purple and green blobs aren't the floating remains of somebody's drink. They're mysterious cells in the brain's visual cortex called oligodendrocyte precursor cells (OPCs). The findings are published in the journal *Nature Protocols*.

The visual cortex processes everything we see. Incoming visual information is relayed to this outer layer of the brain via synapses—the silver streaks above. When the brain's neural circuits are first wired up, more connections, or synapses, are created than needed. As the brain accumulates new experiences and information, OPCs shape neural circuitry by pruning unnecessary synapses.

"OPCs are doing all sorts of things in the brain that help it to function in a normal, healthy way," CSHL Assistant Professor Lucas Cheadle says. OPCs are a specialty of the Cheadle lab. He and his team discovered OPCs' function as neural landscapers in 2022. Before that, they were thought only to produce oligodendrocytes, cells that sheath and support neurons. Now, Cheadle has developed new ways to zoom in and see OPCs in action.

"We're able to see what thousands of OPCs, and even smaller groups of 30–50, are doing," he explains. "From there, we can figure out which synapses are fully engulfed by an OPC, which are in the process of being pruned, and which have maybe just been checked on by an OPC but not processed."

The new techniques used to produce the image above have become essential tools in Cheadle's ongoing work. He and his team are now building on their 2022 discovery to help paint a complete picture of OPCs' role in health and disease.

Cheadle explains, "These mysterious cells are one of the primary sources of glioma," a deadly brain cancer. "They're potentially involved in Alzheimer's disease as well."

It'll take more research to illustrate these connections in detail. In the meantime, Cheadle is eager to share his lab's new tools with researchers around the world.

"The brain is constantly changing, and the same approaches you'd use to look at one type of cell can't just be applied across the board," he says. "We're adapting and innovating to keep up with it—to better understand how the brain works."

More information: Jessica A. Kahng et al, High-confidence and high-throughput quantification of synapse engulfment by oligodendrocyte precursor cells, *Nature Protocols* (2024). DOI: 10.1038/s41596-024-01048-1

Provided by Cold Spring Harbor Laboratory

Erin Yamamoto, M.D., and Juan Piantino, M.D., are among the co-authors of a new study from Oregon Health & Science University that used imaging in neurosurgery patients to definitively reveal the existence of waste-clearance pathways in the human brain known as the glymphatic system. Credit: OHSU/Christine Torres Hicks

Scientists have long theorized about a network of pathways in the brain that are believed to clear metabolic proteins that would otherwise build up and potentially lead to Alzheimer's and other forms of dementia. But they had never definitively revealed this network in people—until now.

A study involving five patients undergoing brain surgery at Oregon Health & Science University provides imaging of this network of perivascular spaces—fluid-filled structures along arteries and veins—within the brain for the first time.

"Nobody has shown it before now," said senior author Juan Piantino, M.D., associate professor of pediatrics (neurology) in the OHSU School of Medicine and a faculty member of the Neuroscience Section of the Papé Family Pediatric Research Institute at OHSU.

"I was always skeptical about it myself, and there are still a lot of skeptics out there who still don't believe it. That's what makes this finding so remarkable."

The study is published in the *Proceedings of the National Academy of Sciences*.

The study combined the injection of an inert contrasting agent with a special type of magnetic resonance imaging to discern cerebrospinal fluid flowing along distinct pathways in the brain 12, 24 and 48 hours following surgery. In definitively revealing the presence of an efficient waste-clearance system within the human brain, the new study supports the promotion of lifestyle measures and medications already being developed to maintain and enhance it.

"This shows that cerebrospinal fluid doesn't just get into the brain randomly, as if you put a sponge in a bucket of water," Piantino said. "It goes through these channels."

More than a decade ago, scientists at the University of Rochester first proposed the existence of a network of waste-clearance pathways in the brain akin to the body's lymphatic system, part of the immune system. Those researchers confirmed it with real-time imaging of the brains of living mice. Due to its dependence on glial cells in the brain, they coined the term "glymphatic system" to describe it.

However, scientists had yet to confirm the existence of the glymphatic system through imaging in people.

Pathways revealed in patients

The new study examined five OHSU patients who underwent neurosurgery to remove tumors in their brains between 2020 and 2023. In each case, the patients consented to having a gadolinium-based inert contrasting agent injected through a lumbar drain used as part of the normal surgical procedure for tumor removal. The tracer would be carried with cerebrospinal fluid into the brain.

Afterward, each patient underwent magnetic resonance imaging, or an MRI, at different time points to trace the spread of cerebrospinal fluid.

Rather than diffusing uniformly through brain tissue, the images revealed fluid moving along pathways—through perivascular spaces in clearly defined channels. Researchers documented the finding with a specific kind of MRI known as fluid attenuated inversion recovery, or FLAIR.

This type of imaging is sometimes used following the removal of tumors in the brain. As it turns out, it also revealed the gadolinium tracer in the brain, whereas the standard MRI sequences did not.

"That was the key," Piantino said.

"You can actually see dark perivascular spaces in the brain turn bright," said co-lead author Erin Yamamoto, M.D., a resident in neurological surgery in the OHSU School of Medicine. "It was quite similar to the imaging the Rochester group showed in mice."

Clearing the waste from the brain

Scientists believe this network of pathways effectively flushes the brain of

metabolic wastes generated by its energy-intensive work. Wastes include proteins such as amyloid and tau, which have been shown to form clumps and tangles in brain images of patients with Alzheimer's disease.

Emerging research suggests medications that may be useful, but much of the focus around the glymphatic system has revolved around lifestyle-based measures to improve the quality of sleep, such as maintaining a regular sleep

schedule, establishing a relaxing routine, and avoiding screens in the bedroom before bed. Especially at night during deep sleep, researchers believe a well-functioning glymphatic system efficiently carries waste proteins toward veins exiting the brain.

"People thought these perivascular spaces were important, but it had never been proven," Piantino said. "Now it has."

The authors credited the late Justin Cetas, M.D., Ph.D., who initiated the study as an OHSU neurosurgeon before leaving OHSU to become chair of neurological surgery at his alma mater, the University of Arizona Health Sciences Center in Tucson. He died in a motorcycle accident in 2022.

More information: Piantino, Juan, The perivascular space is a conduit for cerebrospinal fluid flow in humans: A proof-of-principle report, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2407246121. www.pnas.org/cgi/doi/10.1073/pnas.2407246121

Provided by Oregon Health & Science University

The brain has a waste-disposal system that clears away junk proteins that contribute to the development of dementia and Alzheimer's disease, a new study finds.

Advanced imaging scans have revealed a network of fluid-filled structures along arteries and veins within the brain, researchers reported Monday in the Proceedings of the National Academy of Sciences.

These structures allow cerebrospinal fluid to flow through the brain, potentially flushing out waste proteins like amyloid and tau, researchers said.

Those toxic proteins build up in the brains of Alzheimer's patients, creating plaques and tangles that are hallmarks of the disorder.

Previous research found these sort of fluid channels in the brains of mice, but this is the first time they've been confirmed to exist in humans as well, researchers said.

"Nobody has shown it before now," said senior researcher Dr. Juan Piantino, an associate professor of pediatric neurology in the Oregon Health & Science University (OHSU) School of Medicine.

"This shows that cerebrospinal fluid doesn't just get into the brain randomly, as if you put a sponge in a bucket of water," Piantino added in a university news release. "It goes through these channels."

For the study, researchers injected five patients undergoing brain surgery at OHSU with a tracer that would be carried with cerebrospinal fluid into the brain.

The research team then used MRI scans to track the spread of the tracer throughout the brain.

Images showed that the fluid moved along clearly defined channels in the brain, which researchers called "perivascular spaces."

"You can actually see dark perivascular spaces in the brain turn bright," said co-lead researcher Dr. Erin Yamamoto, a resident in neurological surgery in the OHSU School of Medicine.

Researchers believe the pathways help flush out waste that's been generated by the brain, similar to the way that the lymphatic system flushes waste generated by the immune system throughout the body.

"People thought these perivascular spaces were important, but it had never been proven," Piantino said. "Now it has."

Future research can focus on ways to improve this waste-disposal system in the brain, researchers noted.

For example, quality sleep is believed to help the system better flush waste proteins out of the brain, they said.

More information

The Alzheimer's Association has more on amyloid beta.

New research suggests vulnerable spot in blood-brain barrier allows microplastic penetration — here's what we know

New research indicates that microplastics may be able to get into our brains when we breathe. According to a study by researchers at the Freie Universität Berlin and the University of São Paulo, which was published in the journal PubMed, microplastics can enter our brains via the olfactory nerves and olfactory bulb.

What's happening?

While previous research had indicated that microplastics were entering human bodies through eating and drinking, breathing them into our lungs, and absorbing them into our skin, this new research shows we could be absorbing microplastics directly into our brains when we breathe.

"This case series provides evidence of MPs found in the human olfactory bulb, suggesting a potential pathway for the translocation of MPs to the brain," the researchers wrote. "The findings underscore the need for further research on the health implications of MP exposure, particularly concerning neurotoxicity and the potential for MPs to bypass the blood-brain barrier."

A study from researchers at the University of New Mexico in early 2024 also found a surprising amount of microplastics in peoples' brains.

"It's pretty alarming," lead author Matthew Campen, a toxicologist and professor of pharmaceutical sciences at UNM, said. "There's much more plastic in our brains than I ever would have imagined or been comfortable with."

Why are microplastics concerning?

Plastic does not biodegrade naturally. Instead, it breaks down into smaller and smaller pieces that never really go away. The resulting tiny particles are called microplastics, and they exist forever in the environment — and in our bodies.

What's being done about microplastics?

The easiest and most consequential steps we can take in our everyday lives to avoid microplastics entering our bodies are to stop eating and drinking from plastic containers. Avoiding plastic water bottles and single-use tea bags can lower your exposure.

However, as these studies have shown, microplastics can still enter your body just by breathing, which is not something that you can or should avoid doing. That's why it's so crucial that we drastically decrease the amount of new, virgin plastic our society produces.

Researchers built a 3D image of nearly every neuron and its connections within a small piece of human brain tissue. This version shows excitatory neurons colored by their depth from the surface of the brain. Blue neurons are those closest to the surface, and fuschia marks the innermost layer. The sample is approximately 3 millimeters wide.© Google Research & Lichtman Lab (Harvard University). Renderings by D. Berger (Harvard University)

Researchers have mapped a tiny sliver of the human brain on an unprecedented scale, vividly detailing each brain cell, or neuron, and the intricate networks they form with other cells.

The groundbreaking brain map, which was constructed by Harvard and Google researchers, reveals roughly 57,000 neurons, 9 inches (230 millimeters) of blood vessels and 150 million synapses, or the connection points between neurons.

Dr. Jeff Lichtman, a professor of molecular and cellular biology at Harvard University who co-led the 10-year-long project, said he couldn't believe the detailed map when he first saw it. "I had never seen anything like this before," he told Live Science.

The human brain is a vastly complex organ with about 170 billion cells, including 86 billion neurons. Researchers have previously peeked into the brain at the scale of millimeters using magnetic resonance imaging (MRI). And more recently, advanced microscopy techniques have revealed details at a much smaller scale, improving our understanding of the brain's inner workings.

Related: Most detailed human brain map ever contains 3,300 cell types

Now, using these microscopy methods and an artificial intelligence (AI) system called machine learning, Lichtman and his colleagues have created a 3D map from a piece of brain at the scale of a nanometer, or 1-millionth of a millimeter. This presents a picture of the organ at the highest resolution scientists have ever achieved.

The resulting cell atlas, described in the journal Science on May 9, is also available for scientists to peruse online.

This map charts a tiny piece of brain with a volume of about 1 cubic millimeter — smaller than a grain of rice. A whole adult brain is a million times larger.

The brain fragment was sampled from a 45-year-old woman who had undergone brain surgery to treat epilepsy. Doctors removed the piece from the cerebral cortex, the outermost portion of her brain. After fixing the sample in preservatives, the researchers stained it with heavy metals to help them see the cells. They then embedded the tissue in resin and cut it into more than 5,000 slices, each measuring about 30 nanometers in thickness.

"That's about a thousandth the thickness of a hair strand," Lichtman said.The team scanned each of the slices with a high-speed electron microscope, which uses multiple beams of electrons to illuminate cells in the sample. They then sent the microscopy data to Google for further analysis using AI.

Google's researchers used machine-learning models to identify the same object in different microscopic images and then create a 3D rendering of every object in all the images. They then electronically stitched the renderings together to reconstruct the whole sample in three dimensions. The final 3D map contains a mammoth 1.4 petabytes, or 1 million gigabytes, of data.

"The amount and complexity of the data generated in this project required Google's ability to develop state of the art machine learning and AI algorithms to reconstruct the 3D connectome," Viren Jain, a senior staff scientist at Google who co-led the project, told Live Science in an email.

The scientists' detailed map contains several surprises. For instance, they found that some of the neurons' outgoing wires, or axons, wrapped themselves into knots, forming whorls that Jain described as "mysterious but beautiful." The team also found rare connections between neurons, in which singular axons were linked to up to 50 synapses.

"We're still investigating the function of these connections, but they could explain how very fast responses, or very important memories are encoded," Jain told Live Science.

It remains to be seen whether the whorls and super-strong synapses have anything to do with the tissue donor’s epilepsy, or if they'd be seen in brains of people without the condition, Lichtman noted. He added that the team is now examining brain tissue from a person with Parkinson's, so that may start to address the question.

He added it's unlikely that brain tissue samples from any two people will look exactly the same, in part because the way the brain wires itself depends on an individual's experiences.

The team next aims to map the entire brain of a mouse, which would be 500 times the size of this human brain sample. They're starting with the hippocampus, a key region for learning and memory.

"We have already begun the ambitious task," Lichtman said.

Credit: CC0 Public Domain

Most neurons in the human brain last a lifetime, and for good reason.

Intricate, long-term information is preserved in the complex structural relationships between their synapses. To lose the neurons would be to lose that critical information—that is, to forget.

Intriguingly, some new neurons are still produced in the adult brain by a population of cells called neural stem cells. As brains age, however, they become less and less adept at making these new neurons, a trend that can have devastating neurological consequences, not just for memory, but also for

degenerative brain diseases such as Alzheimer's and Parkinson's and for recovery from stroke or other brain injury.

A new Stanford Medicine study, published Oct. 2 in *Nature*, sheds hopeful new light on how and why neural stem cells, the cells behind the generation of new neurons in the adult brain, become less active as brains age.

The research also suggests some intriguing next steps in addressing old neural stem cell passivity—or even stimulating neurogenesis, the production of new neurons, in younger brains in need of repair—by targeting newly identified pathways that could reactivate the stem cells.

Anne Brunet, Ph.D., professor of genetics, and her team used CRISPR platforms, molecular tools that allow scientists to precisely edit the genetic code of living cells, to conduct a genome-wide search for genes that, when knocked out, increase the activation of neural stem cells in cultured samples from old mice, but not from young ones.

"We first found 300 genes that had this ability— which is a lot," emphasized Brunet, the Michele and Timothy Barakett Endowed Professor. After narrowing the candidates down to 10, "one in particular caught our attention," Brunet said. "It was the gene for the glucose transporter known as the GLUT4 protein, suggesting that elevated glucose levels in and around old neural stem cells could be keeping those cells inactive."

Dynamic brains

There are parts of the brain, such as the hippocampus and the olfactory bulb, where many neurons have shorter lives, where they regularly expire and may be replaced by new ones, said Tyson Ruetz, Ph.D., a formal post-doctoral scholar in Brunet's lab and the lead author of the *Nature* paper.

"In these more dynamic parts of the brain, at least in young and healthy brains," he said, "new neurons are constantly being born and the more transient neurons are replaced by new ones."

Ruetz, now the scientific advisor and co-founder of ReneuBio, developed a way to test the newly identified genetic pathways in vivo, "where the results really count," Brunet said.

Ruetz took advantage of the distance between the part of the brain where the neural stem cells are activated, the subventricular zone, and the place the new cells proliferate and migrate to, the olfactory bulb, which is many millimeters away in a mouse brain.

By knocking out the glucose transporter genes in the former, waiting several weeks, then counting the number of new neurons in the olfactory bulb, the team demonstrated that knocking out the gene indeed had an activating and proliferative effect on neural stem cells, leading to a significant increase in new neuron production in living mice.

With the top intervention, they observed over two-fold increase in newborn neurons in old mice.

"It's allowing us to observe three key functions of the neural stem cells," Ruetz said. "First, we can tell they are proliferating. Second, we can see that they're migrating to the olfactory bulb, where they're supposed to be. And third, we can see they are forming new neurons in that site."

The same technique could also be applied to studies of brain damage, Ruetz said. "Neural stem cells in the subventricular zone are also in the business of repairing brain tissue damage from stroke or traumatic brain injury."

'A hopeful finding'

The glucose transporter connection "is a hopeful finding," Brunet said. For one, it suggests not only the possibility of designing pharmaceutical or genetic therapies to turn on new neuron growth in old or injured brains, but also the possibility of developing simpler behavioral interventions, such as a low carbohydrate diet that might adjust the amount of glucose taken up by old neural stem cells.

The researchers found other provocative pathways worthy of follow-up studies. Genes relating to primary cilia, parts of some brain cells that play a critical role in sensing and processing signals such as growth factors and neurotransmitters, also are associated with neural stem cell activation.

This finding reassured the team that their methodology was effective, partly because unrelated previous work had already discovered associations between cilia organization and neural stem cell function. It is also exciting because the association with the new leads about glucose transmission could point toward alternative avenues of treatment that might engage both pathways, Brunet said.

"There might be interesting crosstalk between the primary cilia—and their ability to influence stem cell quiescence, metabolism and function—and what we found in terms of glucose metabolism," she said.

"The next step," Brunet continued, "is to look more closely at what glucose restriction, as opposed to knocking out genes for glucose transport, does in living animals."

More information: Anne Brunet, CRISPR–Cas9 screens reveal regulators of ageing in neural stem cells, *Nature* (2024). DOI: 10.1038/s41586-024-07972-2. www.nature.com/articles/s41586-024-07972-2

Provided by Stanford University Medical Center

Old people can produce as many new brain cells as teenagers© Organically Human

Research contradicts decades-old theory that humans stop producing neurons in adulthood

Elderly people grow as many new brain cells as teenagers, according to a new study which counters previous theories that neurons stop developing after adolescence.

Healthy men and women continue to produce new neurons throughout life, suggesting older people remain more cognitively and emotionally intact than previously believed, researchers found.

For decades it was thought that adult brains were hard-wired and unable to form new cells.

But a Columbia University study found older people continued to produce neurons in the hippocampus – a part of the brain important for memory, emotion and cognition – at a similar rate to young people.

Researchers examined the brains of 28 previously healthy people who died suddenly between the age of 14 and 79.

“We found that older people have similar ability to make thousands of hippocampal new neurons from progenitor cells as younger people do,” said the study's lead author Maura Boldrini, associate professor of neurobiology.

"We also found equivalent volumes of the hippocampus across ages."

The ability to generate new hippocampal cells, a process known as neurogenesis, declines with age in rodents and primates.

Declining production of neurons and shrinkage of parts of the brain which help form of new episodic memories were believed to occur in ageing humans as well, explaining why younger people find it easier to learn skills and languages.

But the Columbia University study found similar numbers of newly formed cells in old and young brains.

However, the researchers also noted fewer blood vessels and connections between cells in the older brains, which Ms Boldrini said "may be linked to compromised cognitive-emotional resilience" in the elderly.

The findings, published in the journal *Cell Stem Cell*, are likely to be hotly debated.

They come just a month after a University of California study suggested adults do not develop new neurons.

Shawn Sorrells and Mercedes Paredes, who co-authored that research, said: "For now, we do not think this new study challenges what we have concluded from our own recently published observations: if neurogenesis continues in the adult human hippocampus, it is an extremely rare phenomenon."

However, other scientists said the Columbia University findings were promising and could be helpful in developing new treatments for neurological conditions such as Alzheimer's Disease.

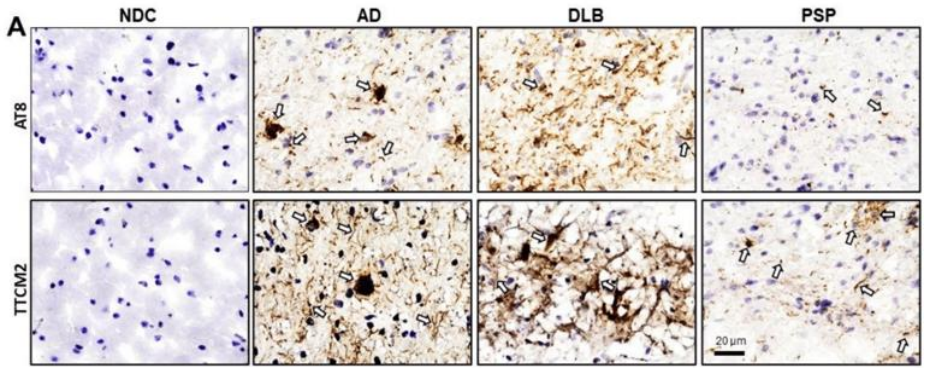
Written by: Chris Baynes

Researchers at the University of Texas Medical Branch (UTMB) recently revealed a groundbreaking discovery in the fight against neurodegenerative diseases like Alzheimer's and dementia.

This new study, published in Science Translational Medicine, presents an innovative nasal spray treatment that has shown promising results in clearing harmful tau protein build-up and improving cognitive functions in aged mice models.

"This nasal spray approach opens new avenues for non-invasive delivery of tau therapeutic antibodies directly to the brain, and it holds promise for many neurodegenerative diseases," said Dr. Rakez Kayed, lead author and professor at the Department of Neurology at UTMB.

Tau is a microtubule-associated protein found in the brain that helps stabilize microtubules, which are part of the framework that maintains cell shape and organization in neurons. In healthy brains, tau proteins keep things orderly.



Representative images of TTCM2 and AT8 immunohistochemical (IHC) staining in fixed frontal cortex sections from AD, DLB, PSP and NDC brain tissues. (CREDIT: Science Translational Medicine)© The Brighter Side of News

However, in neurodegenerative diseases, they can become abnormally twisted and form tangles that disrupt neuronal function and lead to cognitive decline. Current tau immunotherapies have struggled with efficacy due to their limited ability to penetrate the intracellular compartments where these tau buildups reside.

Kayed and his team developed a specific type of antibody, TTCM2, which selectively recognizes and targets toxic tau buildup. This antibody was packaged in particles to enhance its delivery to the brain via the nasal route.

This method bypasses the blood-brain barrier, a significant hurdle in neurodegenerative disease treatment, ensuring rapid and effective delivery of the therapy.

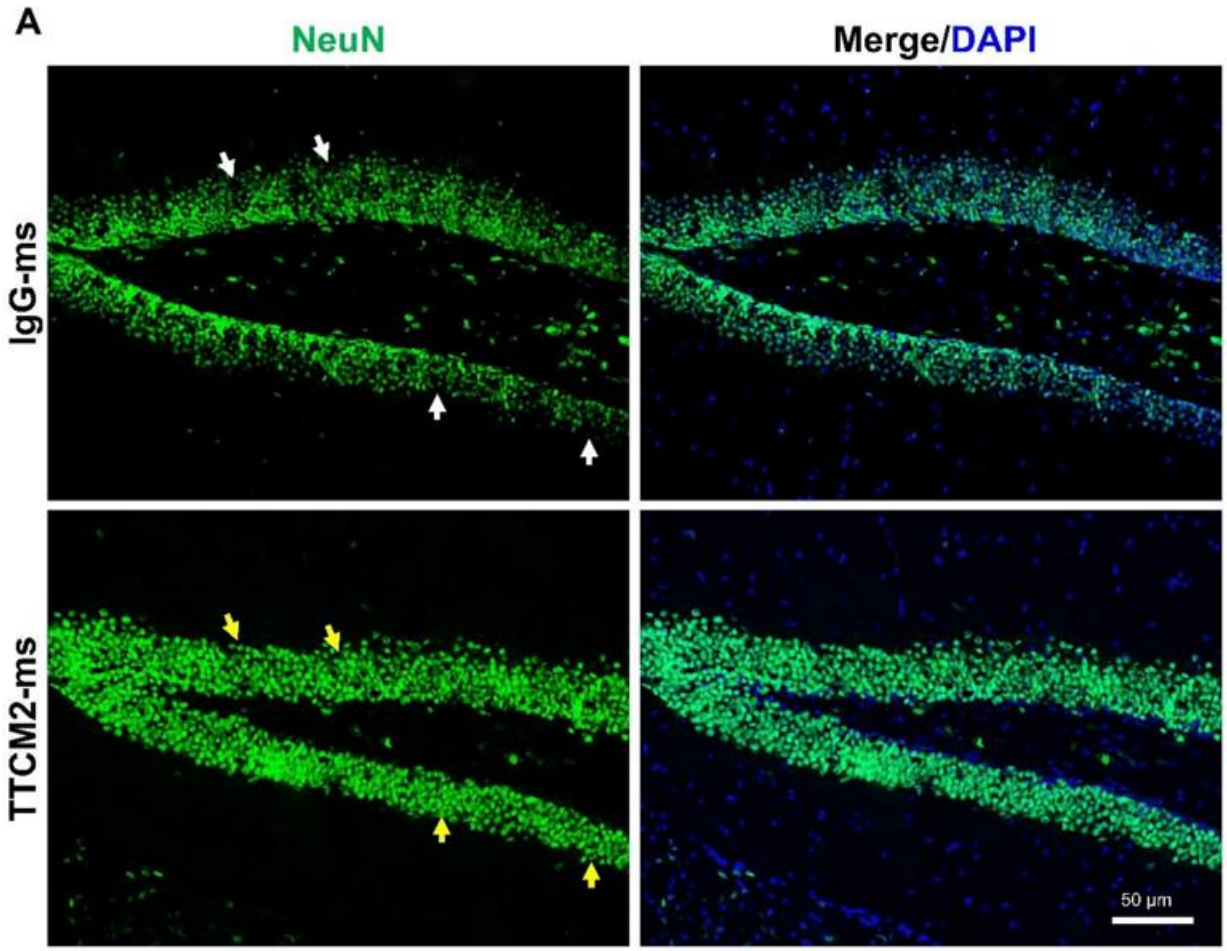
Related Stories

Scientists identify the part of the brain tied to experiencing religion and spirituality New discovery could boost brain metabolism and restore cognitive function in Alzheimer's patients Memory capacity of the human brain is 10x more than previously thought

"Our research highlights the potential of nasal tau immunotherapy to effectively target intracellular tau aggregates—a primary driver of neurodegeneration and cognitive decline in diseases like Alzheimer's and other tauopathies," added Kayed. "This method not only improves the delivery of therapeutic antibodies but also enhances their efficacy in clearing tau aggregates and improving cognitive functions."

A crucial aspect of this approach is the involvement of TRIM21, an intracellular receptor for antibodies and E3 ligase, known for mediating the clearance of antibody-bound pathogens like viruses. In the study, TRIM21 facilitated the clearance of antibody-bound intracellular tau aggregates, thereby enhancing the therapeutic effect and cognitive improvements in the mice model.

"This advancement could significantly impact the treatment strategies for Alzheimer's and related tauopathies, offering new hope for millions of patients suffering from these debilitating conditions," said Sagar Gaikwad, first author of the study and postdoctoral fellow at UTMB.



Representative immunoflourescence staining showing NeuN-positive neurons (green) in brain sections from IgG-ms and TTCM2-ms-treated hTau mice. (CREDIT: Science Translational Medicine)© The Brighter Side of News

The study's findings highlight the potential impact on future treatments for neurodegenerative diseases. UTMB researchers plan to advance this research by conducting further preclinical trials and exploring the potential of TTCM2-ms in human clinical trials. The goal is to translate these promising results into a viable treatment option for patients suffering from Alzheimer's disease and other tau-related disorders.

What causes tau protein build-up in the human brain?

Tau protein build-up in the human brain typically occurs due to abnormal changes in the protein's structure and function. Here's a breakdown of the process:

1. Tau Protein Function: Tau proteins normally play a crucial role in stabilizing microtubules, which are part of the cytoskeleton in neurons. These microtubules

help maintain the structure of the cell and facilitate the transport of nutrients and other molecules within the neuron. 2. Phosphorylation of Tau: Tau proteins are regulated by the process of phosphorylation, where phosphate groups are added to the protein. In a healthy brain, this process is tightly controlled. However, in Alzheimer's disease, tau becomes hyperphosphorylated, meaning too many phosphate groups are added. 3. Aggregation of Hyperphosphorylated Tau: Hyperphosphorylated tau proteins lose their ability to bind to microtubules properly. As a result, they detach and start to accumulate inside neurons, forming aggregates called neurofibrillary tangles (NFTs). These tangles disrupt the normal functioning of neurons, leading to cell damage and death. 4. Genetic and Environmental Factors: Several factors can contribute to the abnormal phosphorylation and aggregation of tau: Genetic mutations: In some cases, mutations in the MAPT gene, which encodes the tau protein, can increase the likelihood of tau dysfunction. Aging: The risk of abnormal tau accumulation increases with age, possibly due to a decline in the brain's ability to clear misfolded proteins. Inflammation: Chronic inflammation in the brain can exacerbate tau pathology by activating enzymes that promote tau phosphorylation. Oxidative stress: Imbalances in free radicals and antioxidants in the brain can lead to tau protein misfolding. Head injuries: Traumatic brain injuries are linked to increased tau accumulation, possibly due to the disruption of normal cellular processes. 5. Spread of Tau Pathology: Once tau proteins start to aggregate, they can spread from one neuron to another, contributing to the progression of Alzheimer's disease. This spread is thought to follow a prion-like mechanism, where misfolded tau induces normal tau to misfold and aggregate. 6. Consequences for Brain Function: The accumulation of tau tangles disrupts the communication between neurons and eventually leads to neuron death. This contributes to the cognitive decline observed in Alzheimer's patients, including memory loss, confusion, and difficulty with problem-solving.

Understanding the precise mechanisms that lead to tau pathology is a major focus of current Alzheimer's research, with the hope that targeting these processes might offer new therapeutic strategies.

person-with-medical-gloves-handling-microplastics-with-tweezers© Svetlozar Hristov/Getty Images

Microplastics continue to be found in some concerning parts of the human body. A new study published Sept. 16 in the *JAMA Network Open* journal explains how microplastics in the human brain can affect an important part of our daily lives: how we smell.

Researchers in Brazil examined the olfactory bulbs of 15 cadavers and detected the presence of microplastics in the olfactory bulbs of eight of them. The olfactory bulbs, located at the bottom of the brain with one in each nasal cavity, contain different kinds of nerve cells that are responsible for helping us smell. The most common material they found was polypropylene, of the most widely used polymers in plastic products today.

microplastics to reach the brain," study lead author Dr. Thais Mauad told *NBC News* of the research. "We thought that if bacteria can pass through this pathway, microplastics might be able to too."
Unfortunately, the base compound of polypropylene is hard to escape in our everyday lives. "Propylene is everywhere—in furniture, rugs, clothes," Mauad said. "We know the place we are most exposed to particles is indoors, because all of our homes are full of plastic."

Related: Study Finds Microplastics in Testicles, With Possible Fertility Effects

Because the study subjects were deceased, the scientists could only learn so much from the phenomenon. More research needs to be done to investigate just how these microplastics in our olfactory bulbs can actually affect our sense of smell in our lives.

"This case series provides evidence of [microplastics] found in the human olfactory bulb, suggesting a potential pathway for the translocation of [microplastics] to the brain," the authors wrote in the study. "The findings underscore the need for further research on the health implications of [microplastic] exposure, particularly concerning neurotoxicity and the potential for [microplastics] to bypass the blood-brain barrier.

For the first time, scientists have detected microscopic microplastics lodged in the human brain.

Researchers in Germany and Brazil say that 8 out of 15 autopsied adults had microplastics detected within their brain's smell centers, the olfactory bulb.

The particles were likely breathed in over a lifetime, since tiny floating microplastics are ubiquitous in the air.

"So when you breathe through your nose, your olfactory nerve directly samples particles and reacts to the particles that you are inhaling as a direct sensory mechanism," said Dr. Wells Brambl, core faculty for medical toxicology at Long Island Jewish Medical Center in New York City.

"The fact that there's no blood-brain barrier there leads to direct access to the brain and, most importantly, right above the olfactory nerve are the frontal and prefrontal lobes, which are where we believe the seat of consciousness is," added Brambl, who was not involved in the study.

Other studies have already shown that "environmental black carbon particles" from air pollution can be found in the olfactory bulb and, in rare cases, tiny amoeba that can trigger a deadly form of encephalitis are also detected there, the Brazilian researchers noted.

They said the new data "extend the notion that not only black carbon but also microplastics accumulate in the olfactory bulb in humans."

Scientists are concerned that higher levels of microplastics are showing up in human brain tissue© Reach Publishing Services Limited

Tiny plastic shards and fibers were found in the nose tissue of human cadavers, according to a recent study.

The microplastics were discovered in the olfactory bulb, which is the part of the nose that sits at the base of the brain, and is responsible for detecting odors.

Lead study author, Luís Fernando Amato-Lourenço, a postdoctoral microplastics researcher at the Free University of Berlin, explained in an email why the discovery is so concerning.

He said: "Once present in this structure, there can be translocation to other regions of the brain. Translocation depends on several factors, including the shape of the particle, whether it is a fiber or a fragment, its size, and the body's defense mechanisms."

Due to their size and shape, the particles are more likely than fibers to bypass microglia cells in the blood-brain barrier, a membrane that protects the brain and spinal cord from many harmful substances.

A flurry of recent studies have discovered microplastics and nanoplastics in human brain tissue, the testes and the penis, human blood, lung and liver tissues, urine and feces, mother's milk and the placenta.

This past March, a study found that people with microplastics or nanoplastics in their carotid artery tissues were twice as likely to have a heart attack, stroke or die from any cause over the next three years than people who had none. They can also interrupt cellular processes and deposit endocrine-disrupting chemicals such as bisphenols, phthalates, flame retardants, perfluoroalkyl and polyfluoroalkyl substances or PFAS, and heavy metals.

Microplastics can be ingested through many foods, drinking water, teabags, many items that are sold in plastic packaging.

Microplastics Found Capable of Crossing the Blood-Brain Barrier, Study Shows©Image Credit: SIVStockStudio & Triff/Shutterstock

Recent scientific discoveries have unveiled a disturbing reality about microplastics, the microscopic plastic particles that have become ubiquitous in our environment. These nearly invisible fragments are no longer confined to our oceans and soil; they have infiltrated the human body in alarming and unexpected ways.

In fact, a 2024 study revealed the presence of microplastics in human testicles, highlighting the extent of this issue [1]. This finding has sparked intense scientific interest, prompting researchers to investigate whether these particles could potentially breach an even more critical barrier: the human brain.

As scientists research this issue, their findings are shedding light on the potential consequences of our plastic-dominated world. Here's what they've uncovered so far.

Potential breakthrough as scientists claim two people communicated in their DREAMS in world first

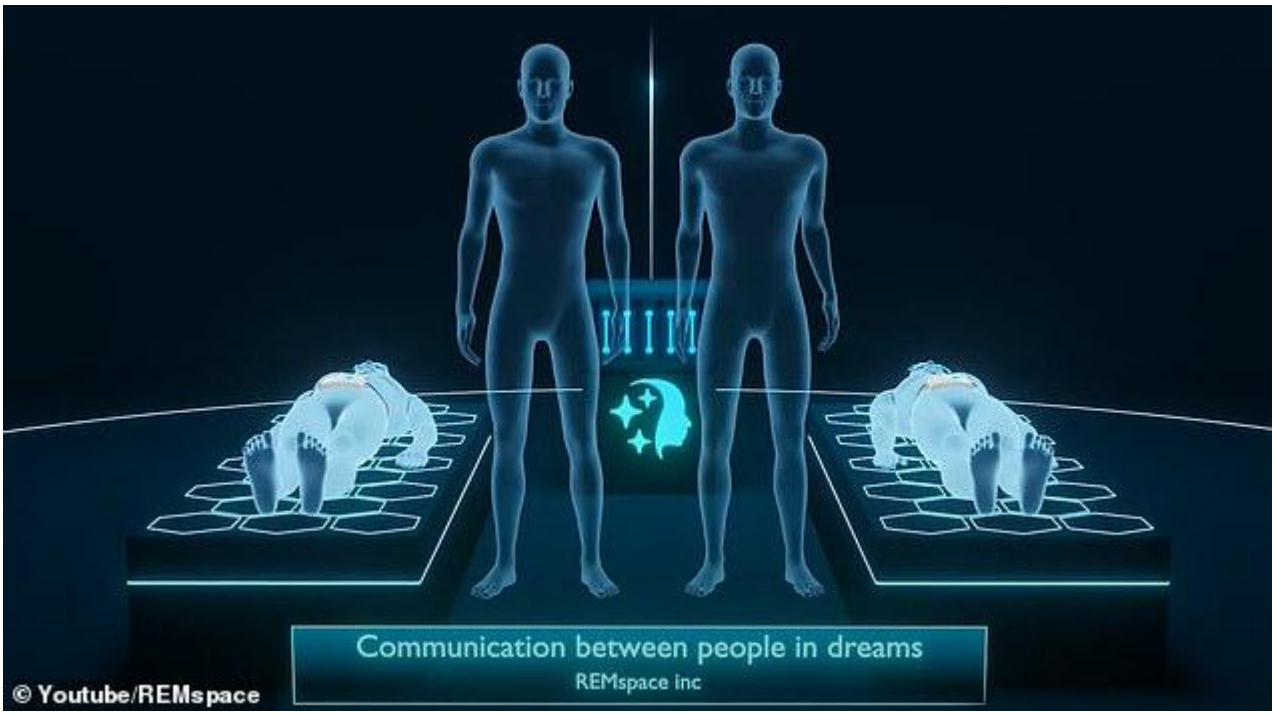
- **READ MORE: These three tricks could allow you to try lucid dreaming**

By ELLYN LAPOINTE FOR DAILYMAIL.COM

Scientists have brought science fiction one step closer to reality by achieving the first two-way communication between individuals during **lucid dreaming**.
In an experiment that sounds like a scene out of the movie 'Inception,' REMspace - a California-based startup that designs technology to enhance sleep and lucid dreaming - reportedly exchanged a message between two people who were asleep.

The company used 'specially designed equipment' which included a 'server,' an 'apparatus,' 'Wifi' and 'sensors,' but did not specify the exact technology they used.

The study participants were asleep in separate homes when REMspace researchers beamed a word created through a unique language between them.



A neurotech company claims to have achieved the first two-way communication between individuals during lucid dreaming

REMspace CEO and founder Michael Raduga said: 'Yesterday, communicating in dreams seemed like science fiction.

'Tomorrow, it will be so common we won't be able to imagine our lives without this technology.

'This opens the door to countless commercial applications, reshaping how we think about communication and interaction in the dream world.'

The technology has yet to be reviewed or replicated by scientists. But if validated, it would be a major milestone for sleep research and could provide applications for mental health treatment, skills training and more, REMspace said.

REMspace used 'specially designed equipment' to allow two individuals to successfully exchange a simple message while lucid dreaming, the company claimed.

Lucid dreaming is when a person is aware they are dreaming while still in the dream state.

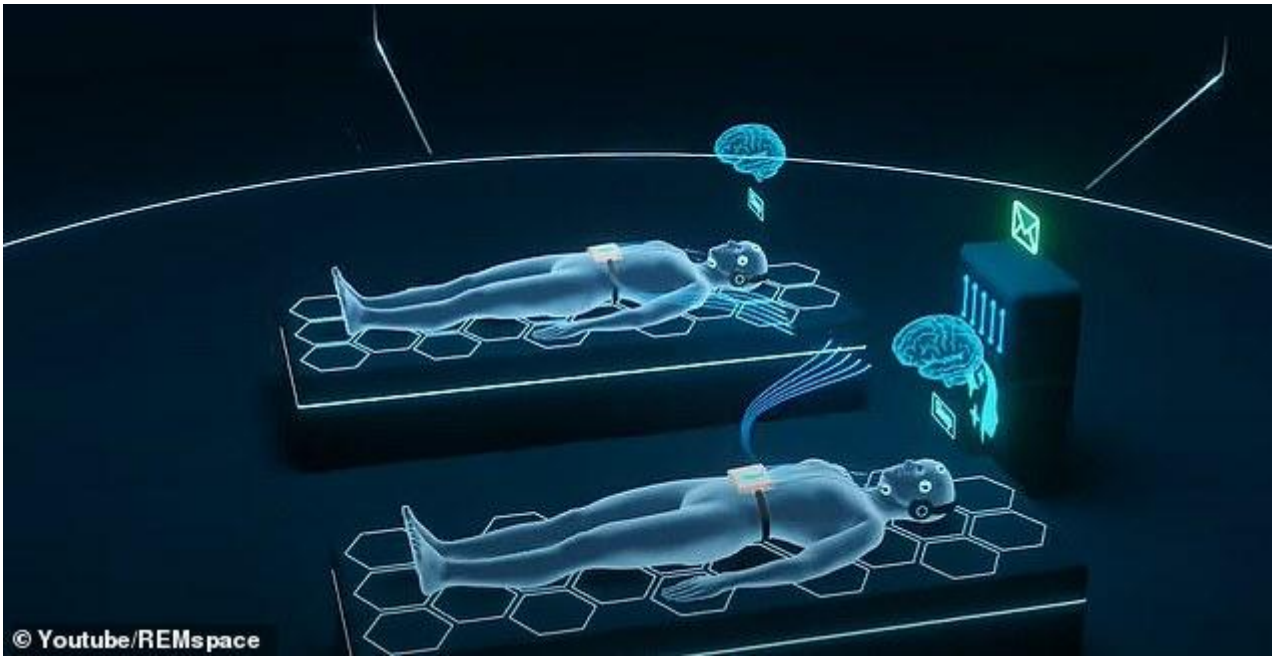
This allows them to perform self-directed actions in their dreams, rather than randomly interacting with the 'dream world' without any sense of control.

This phenomenon happens during REM sleep, or Rapid Eye Movement sleep, when dreaming typically occurs.

REMspace has not revealed exactly what equipment was used in their experiment, but said the experiment involved an 'apparatus' that tracked participants brain waves and other biological data during the experiment.

It also involved a 'server' that can detect when participants enter a lucid dream and generate messages that are transmitted to them.

Two study participants slept in separate homes while their brain waves were remotely tracked by the apparatus, which fed data into the server.



Two study participants slept in their homes while their brain waves were remotely tracked by the apparatus, which fed data into the server

Once the server detected that one participant had entered a lucid dream, it generated a random word and transmitted it to him via earbuds

Eight minutes later, the second participant entered a lucid dream. The server transmitted the stored message from the first participant to her, which she repeated upon awakening

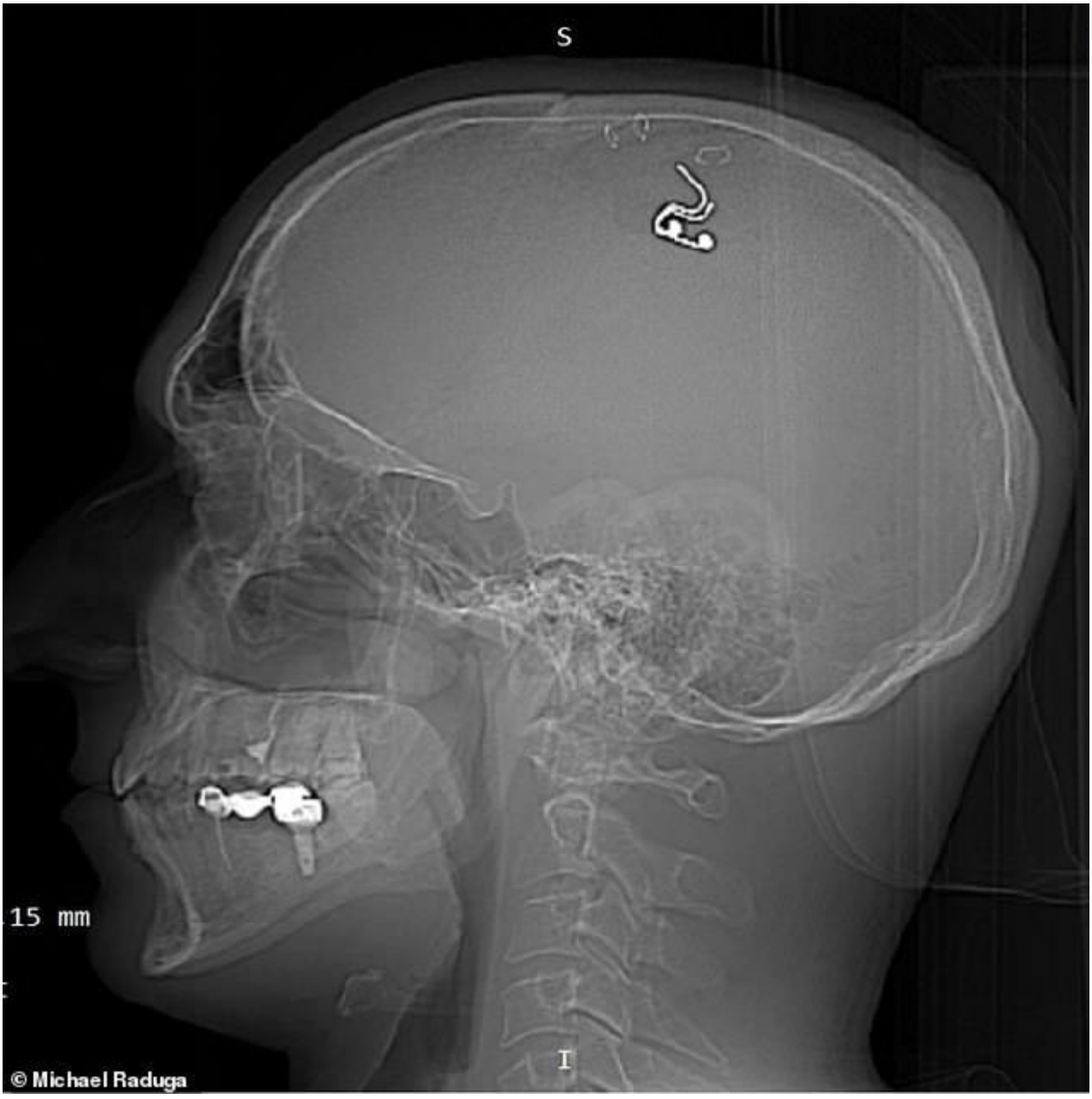
Once the server detected that one participant had entered a lucid dream, it generated a random word from the special language and transmitted it to him via earbuds.

The participant then repeated this word in his dream, and that response was captured and stored in the server.

Eight minutes later, the second participant entered a lucid dream. The server transmitted the stored message from the first participant to her, which she repeated upon awakening.

REMspace was able to repeat this experiment with another pair of participants. But the study will need to undergo rigorous review before the company can definitively say that they achieved dream communication.

Raduga, who is confident about their results, is widely known for his ambitious - and sometimes bizarre - experiments.



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View gallery

The electrode implant is made of platinum and silicon. Raduga claimed that electrical triggers sent to this electrode can influence the course of lucid dreams

In 2023, he put his life on the line when he attempted to implant a microchip in his own brain to control his dreams.

The 40-year-old, who has no neurosurgery qualifications, compared his extremely dangerous experiment to the film of Inception - claiming his 'electrode' one day has the potential to change the course of lucid dreams.

Gruesome footage of the procedure shows him holding his skin back with paper clips while bulldozing the back of his skull using a drill he found at a hardware store.

He inserted the chip into his brain after watching hours of neurosurgery YouTube videos and practicing on five sheep - he told no one of his plans.

The chip was eventually removed in hospital after five weeks.

The highly dangerous study has not appeared in any peer-reviewed journals and is not backed by any universities, but Raduga claimed he needed to do it for himself.

'I am glad I survived but I was ready to die,' he told DailyMail.com in an exclusive interview last year.

Now, he has set his sights on another ambitious goal: enabling real-time communication in lucid dreams.

'We believe that REM sleep and related phenomena, like lucid dreams, will become the next big industry after AI,' Raduga said.

Real-life Inception headband lets you control your dreams - but experts fear zapping the brain with $2,000 device could hinder cognitive abilities during waking hours

- **The Halo AI headband uses high-frequency sound to create lucid dreams**
- **Experts warn that lucid dreams could cause heightened stress**
- **READ MORE: The 10 most common dreams and what they mean**

By NIKKI MAIN SCIENCE REPORTER FOR DAILYMAIL.COM
PUBLISHED: 17:37 EDT, 5 February 2024 | **UPDATED:** 17:37 EDT, 5 February 2024

An **AI** tech startup wants you to trade in regular dreams for a headband that lets you control your nighttime wanderings in a lucid dreamlike state.
Prophetic is releasing the $2,000 Halo AI headband in 2025, which will give wearers unparalleled control over their dreams that could help users grapple with existing problems they're facing in their waking lives.

The headband uses electroencephalography (EEG), which records electrical activity in the brain, and functional magnetic resonance imaging (fMRI) which measures brain activity by measuring the blood flow.

The video player is currently playing an ad.
However, experts aren't yet sure what the long-term effects could be and warn that using high-frequency sounds to zap your brain, could hinder our cognitive ability to process short-term memories.

The Halo AI headband uses EEG and fMRI data to create lucid dreams while you sleep

Experts fear lucid dreams could have negative long-term effects including causing heightened levels of stress and anxiety

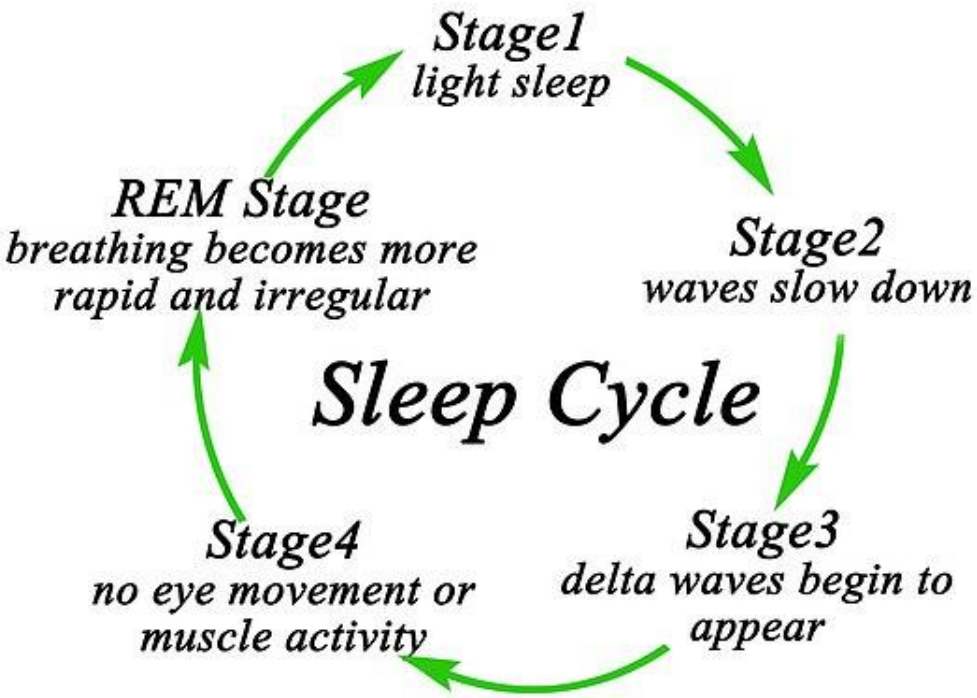
'We are very rarely lucid in our dreams. And not being lucid may be part of, or required, for any effective function of dreams,' Professor Mark Blagrove, a sleep and dream researcher based at the Swansea University Sleep Laboratory, told **Science Focus**.
The EEG and fMRI work together to create a detailed map of the brain to induce lucid dreams which is a state of dreaming where the person is aware they are in a dream while they are sleeping.

Prophetic uses the EEG data to determine when the wearer has entered REM sleep and then uses the fMRI to induce lucid dreams and 'pursue the answers to life's biggest questions,' according to its **site**.
REM, or rapid eye movement, is the state of deep sleep when a person starts dreaming, and the headband can deliver high-frequency sounds to stimulate brain activity so it induces, sustains, and influences lucid dreams.

'It is plausible that the sound stimulation could induce the high-frequency brain activity that is associated with lucidity,' said Professor Mark Blagrove, a sleep scientist based at Swansea University and the co-author of The Science of Art and Dreaming.

'Sound stimulation has been used to induce low-frequency slow waves in slow wave sleep, so the method proposed is credible.'

The wearer won't need to do anything to induce the lucid dreams, instead, 'it will be autonomously happening while you wear the headband,' Prophetic CEO and cofounder Eric Wollberg said in a **demo video** describing how the Halo works.
The caveat to the new AI technology is that scientists don't know what would happen to a person's brain if it is continuously zapped with high-frequency sounds.



REM sleep cycle is when you are in the deepest part of your sleep state and you begin to dream

The Halo AI headband will go on sale in the Fall of 2025 for an estimated $2,000

Scientists believe dreams have basic functions that are essential to our cognitive development including processing emotional experiences, and some fear if dreams are altered, it could interfere with the purpose of the dream.

Lucid dreams could also have detrimental effects on a person's reality, appearing similar to nightmares and sleep paralysis.

According to the **Sleep Foundation**, 'prolonged and intense lucid dreaming may overstimulate the dreamer, leading to heightened stress and worsened sleep.'
'In popular media, everyone talks about how lucid dreaming will change your life, and [how] it's so great…[But] almost no one talks about any dangers or caution,' Nirit Soffer-Dudek, a clinical psychology researcher at Ben-Gurion University of the Negev in Israel told **BBC**, speaking to the negative effects of lucid dreaming.
'I think that more carefulness is needed, in terms of thinking about who this is good for and who it isn't,' Soffer-Dudek added.

Prophetic opened up a beta-test application for its Halo headband last week but is prioritizing people who have already put down a pre-order deposit to receive the device.

- The two Harvard students who put facial recognition AI in Meta's Ray-Ban glasses have big ideas.
- The duo, AnhPhu Nguyen and Caine Ardayfio, are known for their innovative tech projects.
- They plan to apply AI advancements to construction, enhancing robotics with reasoning.

Two Harvard students spooked the world with their demonstration of facial recognition using Meta Ray-Bans. Now, the duo says they have big ideas for AI in the construction industry.

and Anthropic's Claude over the past year have allowed more rapid innovations "in a way that you haven't been able to before," Ardifiyo said.
For example, if an autonomous construction robot trying to dig a hole was blocked by a person standing in the way, it would previously have needed an engineer to hardcode every one of its movements to avoid the person, Ardifiyo said.

But a construction robot with LLM reasoning can say to itself, "I'm going to wait for this person for a couple seconds until they move, and then if they don't, then I'll do this, and you can have a very strong likelihood that whatever it does is pretty reasonable," Adifiyo said.

"That's actually, like, very incredible, and a capability that has only existed in the past six months, essentially," he added.

Privacy concerns have been raised after two Harvard students just demoed a proof-of-concept system called I-XRAY which uses smart glasses to access personal information about others.

The system combines the use of the glasses along with custom software to ID strangers and retrieve personal data about them. The system has been coined 'I-XRAY.'

The students, AnhPhu Nguyen and Caine Ardayfio, took to the social media platform X to share their experiment writing: "Are we ready for a world where our data is exposed at a glance?"

They tested I-XRAY on Harvard's campus and correctly identified random people, before taking it to the subway to test on non-students.

Five technologies have been used and integrated to make the system function. To use it, people simply put the glasses on, then as you walk by people the glasses will detect when somebody's face is in the frame.

synergy between LLMs and reverse face search allows for fully automatic and comprehensive data extraction that was previously not possible with traditional methods alone.
"From the LLM extracted name, a FastPeopleSearch lookup can identify the person's home address, phone number, and their relatives.

The two creators of the system say the tool "quickly highlighted significant privacy concerns."

In a document where they give people the know-how to remove their information from online sources, they write that the purpose of building the system isn't for misuse and will not be released.

"Our goal is to demonstrate the current capabilities of smart glasses, face search engines, LLMs, and public databases, raising awareness that extracting someone's home address and other personal details from just their face on the street is possible today."

While the duo won't be publicly releasing I-XRAY, the demo alone does expose the concerns for privacy and surveillance in the new AI age.

Meta's glasses include a privacy light, but it's not always easily visible.© Photo by Amelia Holowaty Krales / The Verge

Two Harvard students have created an eerie demo of how smart glasses can use facial recognition tech to instantly dox people's identities, phone numbers, and addresses. The most unsettling part is the demo uses current, widely available technology like the Ray-Ban Meta smart glasses and public databases.

Facial recognition tech has been frighteningly accurate for a while now, and I-XRAY is largely just chaining together a bunch of existing technologies. It relies in part on PimEyes, which *The New York Times* described in 2022 as an "alarmingly accurate" face search engine that "anyone can use." Concerns around this tech have been heightened since it came out that Clearview AI was using facial recognition to help law enforcement. What's new about Nguyen and Ardayfio's demo is how the tech is being paired with a consumer gadget that is discreet and easy to access.

"The purpose of building this tool is not for misuse, and we are not releasing it," Nguyen and Ardafiyo write in a document explaining the project. Instead, the students say their goal is to raise awareness that all this isn't some dystopian future — it's all possible now with existing technology. In particular, they point out that I-XRAY is unique because large language models (LLMs) enable it to work automatically, drawing relationships between names and photos from vast data sources.

As you can see from this photo, the privacy light can be very hard to see in outdoor lighting. Even at night.© Photo by Amelia Holowaty Krales / The Verge

Privacy has always been a major concern with smart glasses. Google Glass originally failed due in part to public backlash at being recorded without consent in public spaces. However, it's also true that in the decade since, people have become more accustomed to being filmed due to the rise of smartphones, vloggers, and TikTok. What's unsettling about modern smart glasses, however, is that they don't stand out quite as much as Google Glass did.

Meta Connect 2024 recap: Mark Zuckerberg reveals Orion smart glasses, new AI features, transparent Ray-Bans, and an affordable Quest 3S©Getty/picture alliance

- Mark Zuckerberg kicked off the Meta Connect 2024 developer conference on Wednesday with a keynote.
- The big news was his demo of Meta's first "true AR" prototype glasses, "Orion," which are still a work in progress.
- He also revealed new Meta AI features, limited-edition Ray-Ban smart glasses, and a $299 Quest 3S.

Mark Zuckerberg knocked it out of the park during Meta's big day.

The Meta CEO looked calm, cool, and collected as he took the stage on Wednesday to announce a slew of new AI and hardware products — including a teaser of the company's long-awaited fully holographic glasses, Orion.

The Orion glasses were the news of the day, and in a surprising turn for AR glasses, they looked ... pretty slick!

The smart glasses integrate visuals into the lenses, making them the company's first "true AR" glasses. They still have a ways to go until they truly blend in like Meta's Ray-Ban smart glasses, but they were notably sleeker than the rival Snap Spectacles that Snap CEO Evan Spiegel showed off last week.

Zuckerberg ran a sizzle reel of famous names in tech reacting positively to the Orion glasses in early previews, with Nvidia CEO Jensen Huang to Reddit CEO Steve Huffman praising the prototype as a leap forward.

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But people will have to wait a while to get their hands on them. The current Orion prototype isn't launching to consumers, although Zuckerberg said some external developers get access. It'll be the next version, however, that the company eventually launches to the public.

Zuckerberg's other announcements were more tangible. He showed off limited-edition transparent frames of Meta's Ray-Ban glasses and a slew of new AI features coming to the product, which has been a sleeper hit for the company.

Meta's AI, which is available through Instagram, Facebook, Messenger, and WhatsApp, is also getting new celebrity voices for its chatbots and multi-modal voice and vision features to better compete with OpenAI's ChatGPT.

The CEO covered some of the big names behind the new Meta AI voices, which range from John Cena to Awkwafina. He also demonstrated some impressive real-time assistance tools and debuted a new entry-level Quest 3S mixed-reality headset that costs $299, which will only apply increasing pressure to Apple's rival Vision Pro and its $3,499 price tag.

The keynote was a chance for Zuckerberg to outline his vision of the future — and Meta's role in shaping what could be the next big computing platform.

Wall Street seemed impressed. Meta's stock was up more than 2% as Zuckerberg exited the stage.

Scroll on to get the full recap of Zuckerberg's Meta Connect keynote.

Phones drool, glasses rule. That's the mantra Meta is banking on customers adopting. It starts with updates to the company's smart Ray-Ban glasses, but those may be just a stepping stone to a future with holographic augmented-reality glasses, where people can have more lifelike video calls, watch TV, or read text messages, all while still seeing the world around them.

In a July earnings call, Zuckerberg said the second generation of glasses "continue to be a bigger hit sooner than we expected — thanks in part to AI." People were buying the glasses quicker than the company could make them, he said. The market-intelligence firm International Data Corporation says some 700,000 pairs have been shipped since last October. Meta's Ray-Bans have a camera and speaker and are packed with AI. Updates give the wearer real-time translation if someone is speaking with them in Spanish, English, French, or Italian, and they also have features for everyday use, like remembering where you

parked your car or helping you create an outfit from the clothes in your closet or make a smoothie with the fruits in front of you.

Earning a modicum of cool in what's been panned as perhaps the dorkiest market in tech is a big leap.

They're far from being widely adopted, but Meta hopes this will be the next frontier. Glasses are "a very natural computing platform," Zuckerberg said. The Ray-Bans also have the benefit of being "just good-looking glasses," he told the crowd during Meta's Connect 2024 event, and he said "people want to have something on their face that they're proud of and that looks good."

not expected to sell more than 500,000 devices this year (in comparison, some 500,000 iPhones are sold globally every *day*). Its $3,500 price point is certainly a deterrent to widespread adoption, but so is the feasibility; they're clunky, there are too few programs made for them, and they're stuck among a niche user. VR headsets are "not going to be mass market, ever, in this current form," says George Jijiashvili, the senior principal analyst of games at the research firm Omdia. But if Meta's can make AI work in a way that combines video capture, sound, and location context together, the glasses could be a game changer. "If they manage to create an AI solution that actually works very well, then having glasses in that situation makes a lot of sense. You can see the road to mass adoption more clearly with glasses than with VR headsets."

That's what Zuckerberg hopes, too. Even though the Orion glasses won't be sold anytime soon, if ever (Zuckerberg acknowledged they have to become more stylish and affordable), he's trying to drum up excitement, and, as my colleague Peter Kafka noted, convince the world that he can build the future of computing. "These glasses exist. They are awesome," Zuckerberg said. "They are a glimpse of a future that I think is going to be pretty exciting." So far, it's been hard to convince the average person they need a computer strapped to their face. But a fancy version of the same specs worn by Bob Dylan, Lady Gaga, and countless other celebrities who arguably bring more cool cache than a founder wearing an oversize T-shirt emblazoned with "Either Zuck or nothing" in Latin at a product launch may be the way to start.

Smart glasses, an arguably niche but rapidly advancing category of wearable devices that allows users to interact with digital content while keeping their eyes on the real world, will largely replace smartphones as the world's primary computing platform by the end of the decade, according to the latest word from Mark Zuckerberg, co-founder, chairman, and CEO of Meta. Zuckerberg, who is partially known for having dropped out of Harvard after creating a successful platform called Facebook, shared the prediction last week following the introduction of Orion, Meta's first true augmented reality glasses. A look at Orion, including Zuckerberg's thoughts, can be found below.

What I think is going to happen with glasses is that we're going to get to this point, probably sometime in the 2030s, where you have your phone with you, but it's going to stay in your pocket more, because you're going to be doing more and more things on your glasses than maybe today you'd do on your phone. The glasses will be your main computing platform, and that will be kind of your default, go-to thing.

It's official; we're living in a dystopian nightmare, only without any of the cool clothes or neon-covered megacities. As first reported by 404 Media, two Harvard students recently proved that it was possible to knock together some software that can turn a pair of Ray-Ban Meta smart glasses into a face recognition doxxing tool.

PimEyes offers a fairly simple opt-out process which involves uploading a photo of yourself . PimEyes will then remove any photos that are a match in its database. The original images will still exist on whichever websites they were scraped from, but anyone making a search for your face using PimEyes will no longer find any matching results.

1. Visit the PimEyes website.
2. At the top of the screen, select **Opt-out**.
3. Click **Upload photo**.

4. You should choose high-quality photos that are full-face, well-lit, and with nothing covering your face or eyes.
5. For the best results, upload multiple photos that give different angles of your face.
6. Agree to the terms and confirm that you are over 18, then click **Next**.
7. Upload a scan or photograph of a government issued ID. You should blur or cover any personal information such as your name, address, and any other personal information. Make sure that the photograph and expiry date of the ID remains uncovered.
8. Once you have uploaded your ID, enter an email address. This will only be used to send you confirmation that your images have been removed. You can use an email alias for safety if you wish.
9. Once your application has been processed, you should receive an email confirming that your images have been removed from the PimEyes database.

How to remove your photos from FaceCheck

Images are removed immediately but can take five days to be permanently deleted

Instructions to remove photos from FaceCheck website

FaceCheck / Pocket-linet
FaceCheck is another website that offers the ability to search based on an image of a face. Searching for a face will bring up results from other websites that include images of the same face. The results are ranked using a color coding

system, with dark orange results being certain matches, yellow being confident matches, green being uncertain matches, and gray being weak matches.

What Is Doxxing? 5 Ways to Protect Yourself

What is doxxing? The practice, also spelled "doxing," is when netizens use the internet to source and collect someone's personal and private information and then publicly release that information online [source: S-W].

Derived from the word "documents," the term is an abbreviated version of "dropping dox," a method of revenge that dates back to the hacker culture of the early 1990s [sources: Goldman, Honan].

How Doxxing Works

The internet makes it easy to find publicly available information, such as landline phone numbers or mailing addresses, once you know a person's name, and white pages-style directory sites have long replaced old-school phone books.

But doxxing takes things much further than an innocent search for contact information.

Doxxers often set out to tie an anonymous online profile on social media sites to the true identity of the person behind it. They then publicly reveal that person's real name, along with personal details ranging from home addresses and unlisted cell phone numbers to Social Security numbers, the names of family members or bank account details.

Like identity theft, doxxing usually requires a bit of unscrupulous investigation on the part of the person digging up the info, such as stalking the target's social media profiles looking for pets' names, maiden names or other clues that they may use to guess passwords or answer security questions.

Unlike identity theft, however, the goal of doxxing is typically retribution, harassment or humiliation rather than access to financial accounts. Of course, once doxxers reveal a victim's personal details publicly, there's no telling what other internet users may do with them.

Doxxing Victims

Both private and public figures have been "doxxed" and, surprisingly, the practice is often completely legal, especially if the information is in the public domain. However, established communities like Reddit widely frown upon the practice [sources: Honan, Pelisek, S-W].

In 2013, doxxing (both the word and the practice) gained mainstream exposure when celebrities including Beyoncé, Ashton Kutcher and Hillary Clinton had closely guarded information such as their home addresses and cell phone numbers revealed online [source: Pelisek].

More recently, some have used the word "doxxing" — sometimes controversially — to describe the practices of investigative journalists who use techniques associated with doxxing to identify and research the targets of their reporting [sources: Goldman, S-W].

How to Protect Yourself From Doxxing

Doxxing can lead to death threats and people showing up to your physical address — actions that may require that you involve law enforcement. To protect yourself from doxxing, you should:

1. **Use a virtual private network.** A VPN can keep your information private that a doxxer would otherwise try to exploit through your internet service provider.

2. **Create better passwords.** Even though it's easier to memorize one password, avoid using the same one for every account. Also, use unique passwords that are not easy to guess.
3. **Hide domain registration information.** This database can contain personal information, like your home address.
4. **Create separate email accounts.** If you use different emails for different parts of your life — for example, financial and social online accounts — an attacker won't have access to all your information.
5. **Keep personal details off the internet.** Don't share your birthdate, hometown or other private information online so that a doxxer cannot easily gain access to your accounts.

Lots More Information

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(Photo credit: DALL·E)© PsyPost

Ever heard a snippet of a song and instantly known what comes next? Or picked up the rhythm of a chorus after just a few notes? New research from the Center for Music in the Brain at Aarhus University and the Centre for Eudaimonia and Human Flourishing at the University of Oxford has found that our brains process music through a specific hierarchical activation of several regions. The findings, published in *Nature Communications*, provide new insights into the neural mechanisms underlying our ability to anticipate and identify familiar melodies.

Following this memorization phase, the participants were subjected to an auditory recognition task while their brain activity was recorded using magnetoencephalography (MEG). MEG is a non-invasive imaging technique that captures the magnetic fields produced by neural activity, providing precise temporal and spatial resolution.

The recognition task consisted of 135 five-tone musical sequences, some of which were identical to the original piece while others were systematically varied. These variations were introduced at different points in the sequence to observe how the brain responds to changes in familiar patterns.

Bonetti and his colleagues found that when participants recognized the original memorized sequences, their brain activity followed a specific hierarchical pattern. This pattern began in the auditory cortex, the region responsible for processing

basic sound information, and progressed to the hippocampus and cingulate gyrus, areas associated with memory and cognitive evaluation.

A rendering of the poppy seed–sized brain of a fly (Drosophila melanogaster)© Tyler Sloan / Amy Sterling / FlyWire / Princeton University

What happened

A consortium of scientists published the first complete map of a fruit fly's brain Wednesday in the journal Nature. Identifying and charting the 130,000 neurons and 50 million connections inside the poppy seed–sized brain of the fly, Drosophila melanogaster, took 10 years and involved hundreds of researchers worldwide.

the first time we've had a complete map of any complex brain," said Mala Murthy, a Princeton neurobiologist who helped lead the FlyWire project, to The New York Times. The "stunning detail" of the "tremendous complexity" packed into the fruit fly's tiny brain could "reveal principles that apply to other species, including humans, whose brains have 86 billion neurons," the Times said.
The "beautiful" and complex "tangle of wiring" mapped out in computer simulations may hold the "key to explaining how such a tiny organ can carry out so many powerful computational tasks," like sight, hearing and movement, the BBC said.

What next?

This "amazing technical feat" paves the way for mapping the neural pathways of "larger brains such as the mouse and, maybe in several decades, our own," brain

researcher Lucia Prieto Godino of London's Francis Crick Institute said to the BBC. A mouse brain "contains about 1,000 times as many neurons as a fly," while the human brains has a million times more, the Times said, and scientists recognize that "bigger brains may not follow" the same "fundamental rules" for sending signals quickly across a fly's brain.

Apple has been stuck in an innovation rut for the past few years. Aside from the Vision Pro headset — which expectedly didn't gain a mass reception — the company hasn't made any notable hardware strides apart from its bread-and-butter mobility and computing portfolio. That could change in the next few years.

For Apple, the inspiration would come from its pricey headset."The plan is to bring the Vision Pro's ability to understand its surroundings to more products," adds the report. But it's going to be a long wait until we see Apple's take on the smart glass category.

The XR wearables industry is at somewhat of a pivotal point. On one hand, we have products like the Meta Quest 3s headset that are bringing premium features like color passthrough to a price point that is nearly one-tenth of what Apple commands for the Vision Pro.

Digital Trends© Provided by Digital Trends

Then we have players like Xreal, Rokid, and RayNeo trying to make smart glasses that don't look like nerdy gizmos. Yet, at the same time, we have giants like Microsoft shutting the doors on ambitious XR products like the HoloLens despite being at the forefront of the AI race.

Meta Ray-Ban glasses can collect data from other people.© meta.com, Meta

Ray-Ban Meta glasses may look like a simple accessory, but their features can be surprising. Two students from Harvard University conducted an experiment that demonstrated how quickly and easily personal

By integrating facial recognition systems, public databases, and artificial intelligence, a glasses user could gather detailed information about people captured by the camera. As the experiment indicates, **Ray-Ban glasses** could become dangerous for obtaining personal data, such as names, addresses, phone numbers, and even insurance policies.

Meta's Orion Glasses: The Future of Augmented Reality Unveiled

It's mea culpa time as the Macalope is here again to talk about Meta, AR glasses, and the icky mess that is humanity. First off, here's to today's college kids! When the Macalope was in college he… well, let's just say mistakes were made. He was decidedly not doing experiments to point out the flaws in modern technology.

And now? We cheer for these new devices. Last week the Macalope wrote about Meta's Orion prototype, taking a look at the variety of opinions about the device. And even he neglected to bring up the privacy issue, focusing instead on the aesthetics. Yes, Meta's Orion pass better for regular glasses than the Vision Pro. Meta's Ray Bans pass even easier for regular glasses.

Is that something we *want*, though? It's all well and good if they're being used for harmless entertainment, walking directions or idly looking up what "brat" is supposed to mean, anyway. But that's not all they're going to be used for.

Remember how Facebook got started.

It all began in 2003, when Facebook founder and CEO Mark Zuckerberg created an online programme called "Facemash," which allowed users to objectify fellow

students by comparing photos of their faces and selecting who they deemed as “hotter.”

Who knew that rewarding someone for making something gross by turning them into a billionaire would be a mistake?

Immediate, in-the-wild privacy violation is simply the next logical step. Social media companies do not care about your privacy except for the way it tastes as it slides past their tongues. So sweet.

Meta Connect 2024 recap: Mark Zuckerberg reveals Orion smart glasses, new AI features, transparent Ray-Bans, and an affordable Quest 3S©Getty/picture alliance

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- The big news was his demo of Meta's first "true AR" prototype glasses, "Orion," which are still a work in progress.
- He also revealed new Meta AI features, limited-edition Ray-Ban smart glasses, and a $299 Quest 3S.

Mark Zuckerberg knocked it out of the park during Meta's big day.

The Meta CEO looked calm, cool, and collected as he took the stage on Wednesday to announce a slew of new AI and hardware products — including a teaser of the company's long-awaited fully holographic glasses, Orion.

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The smart glasses integrate visuals into the lenses, making them the company's first "true AR" glasses. They still have a ways to go until they truly blend in like Meta's Ray-Ban smart glasses, but they were notably sleeker than the rival Snap Spectacles that Snap CEO Evan Spiegel showed off last week.

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Scroll on to get the full recap of Zuckerberg's Meta Connect keynote.

- Meta's Reality Labs is exploring all kinds of wearable AI tech, CTO Andrew Bosworth says.
- Its projects include camera earbuds and mixed-reality goggles.
- Reality Labs, known for VR and AR, has also faced budget cuts and layoffs.

The rapid advancement of wearable technology is making it easier to accessorize with incorporate AI.

But the cuts haven't stopped Reality Labs from dabbling in new ideas. Behind the scenes, Reality Labs has many projects, from camera earbuds to mixed reality goggles. "If there's a concept that you could imagine, we either have had or do have somebody building a thing around it," Bosworth told Command Line.

Reality Labs uses a step-by-step process to develop products from concept to release, Bosworth said. It begins with a pre-discovery team that prototypes new ideas, which are then reviewed to select a few for further exploration. After prototyping, successful concepts enter the company's product road map, and about half of those make it through final testing to be released to the public.

The camera earbuds are in an early stage of development, while a pair of "steampunk" mixed reality goggles have advanced to the product release process, Command Line reported.

"We definitely don't want to be outflanked by someone who came up with some clever, integrated wearable that we hadn't thought about," Bosworth said.

Meta did not immediately respond to a request for comment from Business Insider.

- Meta Ray-Ban smart glasses make it easier to document things that happen in your life.
- A new project by two students called I-XRAY showcases what can be done with custom software and a pair of Meta Ray-Bans.
- The app allows almost instant recognition of subjects, with data that includes names, addresses, phone numbers, and more.

Meta makes one of the best smart glasses you'll find on the market, with the Ray-Ban collaboration sitting at the very top of our "best of" list. Of course, this is still a very niche product, which means, you're probably not going to see many of these out in the wild, despite the latest version of these glasses being available for close to a year now. Again, these glasses aren't for everyone, but if you're someone that likes to take photos and videos, and wants to capture the world in a different way, then the Meta Ray-Ban smart glasses are going to be worth trying out.

Ray-Ban Meta Black close-up with charging case in the background© Provided by Android Police

Related

Ray-Ban Meta smart glasses review: Built for social creators

Ray-Ban style meets Meta smarts to create a pair of almost perfect POV glasses for social creators

Now, with the introduction of these types of devices, there will always be privacy concerns. Especially now, with the implementation of AI in lots of modern products, which has led to companies to be very cautious about how their products are portrayed and how each device collects data that's captured. Meta even has a dedicated privacy page that goes through the ins and outs of its Ray-Bans in order to try and better educate its users. Of course, a brand can only control so much, which is why there will always be outlying examples of tech that can be used in ways not originally intended.

This isn't the future, this is our new reality

This is where a project called I-XRAY by two Harvard students comes into play, with AnhPhu Nguyen and Caine Ardayfio giving us real world examples of how the Meta Ray-Bans can be used when some clever tweaks are applied (via The Verge). In a post on X by Nguyen, we can see the work in action, showcasing how a string of available services and a custom application that can process it all, can really make an episode of Black Mirror come to life.

So let me paint a word picture for you (it is my job, after all). I've got two big things to save up for — my wedding and my home. It was all going so well until Meta Connect 2024, when the Zuck came up on stage and showed off the new transparent Ray-Ban Meta smart glasses.

The moment I saw them, I knew it was inevitable. Even if it meant I had to live off instant noodles for the next month, these are *extremely* my vibe. And now that I have one of the 7,500 pairs that Meta sold of this limited edition, zero regrets are felt. These see-through specs are easily the best-looking gadget I've seen in a long time.

Ray-Ban Meta smart glasses (with transition lenses): $379 @ Best Buy These smart glasses far exceed their 12MP camera capture abilities. Meta AI features give them all the smarts to answer any questions about the world around you (thanks to multimodal AI). And all of this is underpinned by a stellar-looking set of specs that feel great to wear all-day round.View Deal

Nothing at all...nothing at all...

((Image credit: Future))

Stupid sexy glasses! There is absolutely nothing new about them — no improvement to the Bluetooth and wi-fi connectivity, no Meta AI for me in the U.K. (unless you use one of the best VPNs to trick them), and no updates to the camera or battery life.

All Meta has done in its love-in with Ray-Ban is house all of the components in a completely transparent frame. And that's all these two needed to do, as it tickles every single of my nerdy itches at once to make this oh-so-divine on my face.

And the most recent additions are set to make these smarter than ever — an updated prompting system with the multimodal AI that understands more natural questions leads the charge. Instead of having to say "hey Meta, look and…" followed by your question, you can word it a lot more naturally.

But everything else coming too makes these a must-buy, from the ability to remember the location of items on request, reading QR codes and calling numbers it sees. Special shout-out to live translation, which is going to be *huge* for a traveler like me.

Outlook

((Image credit: Future))

So while this limited edition is sold out now, I'd still highly recommend you pick up a pair with transition lenses. The capabilities extend super far beyond just being a pair of camera glasses — thanks to all of its AI smarts.

Yes, I may be looking at my bank account and diet of baked beans and feeling a little poor right now, but damn do these look like something special.

Apple smart glasses tipped to launch in 2027 to fight Meta with Visual Intelligence© Martin Hajek/iDropnews)

Following up on a report from February this year, Bloomberg's Mark Gurman is doubling down on claims that Apple is developing new wearable products,

suggesting that it could bring smart glasses and AirPods with cameras to market as early as 2027, as discussed in his latest Power On newsletter.

And while it's hard to say how AirPods with cameras could benefit the average user, Gurman has previously stated that the rumored product "would give consumers many of the benefits of smart glasses without needing lenses and frames."

Of course, if Gurman's report is to be believed, we're a few years out from seeing these products go on sale, we may have to settle for the Apple Intelligence features which are expected to arrive with iOS 18.2 in December.

In the meantime, you can access similar features such as the ability to take photos, record video stories, and access an AI voice assistant via the Ray-Ban Meta smart glasses.

A new study published in *Molecular Psychiatry* has revealed that a single dose of the psychedelic drug 2,5-dimethoxy-4-iodoamphetamine (DOI) can lead to long-lasting changes in brain structure and cognitive flexibility in mice. The researchers found that mice treated with DOI became more attuned to previously overlooked cues, allowing them to learn more efficiently from their experiences. These effects appeared to depend on the timing of drug administration and the animals' experiences after the treatment.

The study, conducted while Sabanovic was a PhD candidate at the University of Oxford, was carried out on young adult mice to assess the structural and cognitive effects of DOI. The researchers administered a single dose of DOI to the mice and then evaluated their behavior using a complex reversal learning task designed to measure cognitive flexibility. This task required the mice to adapt their behavior based on changing reward patterns, allowing the researchers to see how well the animals could learn from both positive and negative outcomes.

In addition to behavioral testing, the researchers performed brain imaging to assess changes in brain structure following DOI treatment. They used magnetic

resonance imaging (MRI) to look for alterations in brain volume, focusing on regions associated with sensory processing and cognitive control. Brain samples were collected from the mice 24 to 36 hours after drug administration to capture the early structural changes, as well as several weeks later to investigate any long-term effects.

In his sci-fi film "Inception," (2010), Christopher Nolan imagined his protagonist slipping into other people's dreams and even shaping their contents. But what if this story wasn't so far away from real life?
Our research suggests that it is possible to interact with volunteers while they are asleep, and even to converse with them at certain key moments.

Lucid dreaming

Most of us only realize we've been dreaming upon waking. Lucid dreamers, on the other hand, have the unique ability to remain aware of the dreaming process during REM sleep, a stage of sleep during which brain activity is closer to that of the waking phase.

Even more surprisingly, lucid dreamers can sometimes exercise partial control over their dream's narrative. They are then able to fly away, make people appear or disappear, change the weather or transform themselves into animals. In short, the possibilities are endless.

Such lucid dreams can occur spontaneously or be engineered by specific training. The existence of lucid dreaming has been known since ancient times, but for a long time it was considered esoteric and unworthy of scientific exploration.

Such views have changed thanks to a clever experiment set up by psychologist Keith Hearne and psychophysiologist Stephen Laberge in the 1980s. These two

researchers set out to prove that lucid dreamers were indeed asleep when they realized they were dreaming.

Adaptive deep brain stimulation trial results poised to “transform” Parkinson’s disease© University of California

A new type of self-adjusting neuromodulation is poised to transform the landscape of neurology, as per analyst reaction to results from two studies evaluating the technology.

The pair of studies, conducted at University of California, San Francisco (UCSF), tested what it calls ‘intelligent brain pacemakers’ – an implant that uses an approach called adaptive brain stimulation (aDBS). This method involves using artificial intelligence (AI) to spot changes in patient symptoms via brain activity monitoring and then delivering personalised care.

The studies “mark a major advancement in the management of Parkinson’s disease” according to GlobalData analysis, which also reflects the growing influence of digital technologies in neurological disease treatment.

The global market for neurological devices was valued at $12.5bn in 2023 and is forecast to reach $20.9 billion by 2033, as per a GlobalData report.

DBS has been a US Food and Drug Administration (FDA)-approved option for Parkinson’s disease patients since 1997. Whilst effective, this type of intervention does not adapt to natural fluctuations in brain activity and cannot account for changes in levels of medications patients take for the disease.

“The big shift we’ve made with adaptive DBS is that we’re able to detect, in real time, where a patient is on the symptom spectrum and match it with the exact amount of stimulation they need,” said Little, associate professor of neurology and a senior author of both studies.

"Adaptive deep brain stimulation trial results poised to “transform” Parkinson’s disease" was originally created and published by Medical Device Network, a GlobalData owned brand.

Microscopic magnetic nanodiscs could provide a much less invasive means of providing deep brain stimulation, a new study says.

The tiny discs -- about 250 nanometers across, or 1/500 the width of a human hair -- would be injected directly into specific regions of a person's brain, researchers say.

From there, researchers said, the discs could be activated by applying a magnetic field outside the patient's body.

Tests in lab mice show that the discs "had an impact on neuron activity and on behavior," researcher Ye Ji Kim, a doctoral student at MIT, said in a news release.

Deep brain stimulation uses electrodes implanted in target brain regions to treat conditions like Parkinson's disease, epilepsy, obsessive-compulsive disorder, tremors and Tourette syndrome, the Mayo Clinic says.

But placing the implants involves major brain surgery, which opens patients up to a number of harmful complications, researchers noted.

These nanodiscs could provide a less invasive alternative to currently used electrodes, researchers said.

The nanodiscs contain a magnetic core and an electrically charged outer shell. When exposed to a magnet, the core presses against the outer shell and causes it to deliver electrical pulses to nearby neurons, researchers said.

Stimulation can be switched on and off by flipping a switch on an electromagnet, researchers said.

The discs successfully stimulated brain regions in mice associated with feelings of reward and motor control, researchers report.

This included the subthalamic nucleus, "the region where electrodes typically get implanted to manage Parkinson's disease," Kim explained.

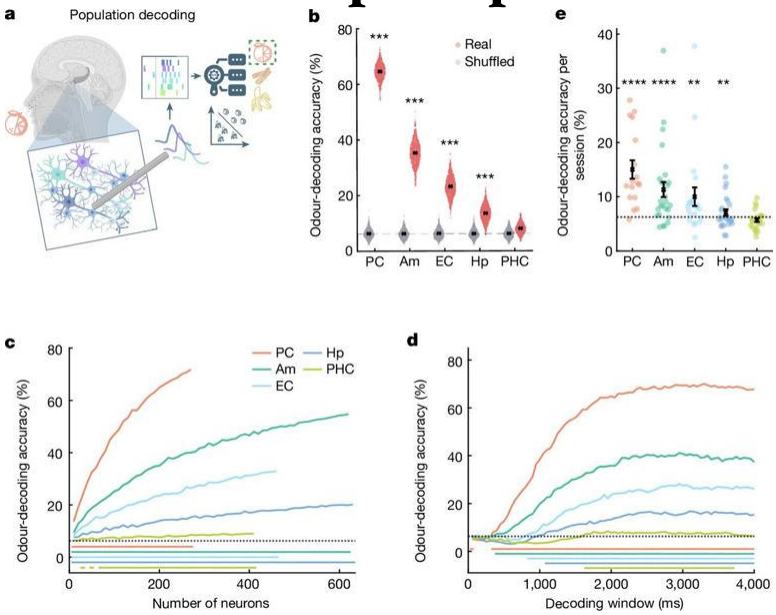
However, researchers say the discs need more work to make them powerful enough to provide the sort of brain stimulation needed to treat human illnesses. And experts stress that research done in animals often has different results in people.

"Yes, it's a record-breaking particle, but it's not as record-breaking as it could be," senior researcher Polina Anikeeva, a professor of materials science and engineering and brain and cognitive sciences at MIT, said in a news release.

"When we find that these particles are really useful in a particular clinical context, then we imagine that there will be a pathway for them to undergo more rigorous large animal safety studies," Anikeeva added.

The new study was published Friday in the journal Nature Nanotechnology.

Another step towards decoding smell: Investigating the neuronal mechanisms of human odor perception



Neuronal activity decodes odor identity. Credit: Nature (2024). DOI: 10.1038/s41586-024-08016-5

We often only realize how important our sense of smell is when it is no longer there: food hardly tastes good, or we no longer react to dangers such as the smell of smoke. Researchers at the University Hospital Bonn (UKB), the

University of Bonn and the University of Aachen have investigated the neuronal mechanisms of human odor perception for the first time.

While the activity of nerve cells in the olfactory cortex most accurately predicted which scent was smelled, neuronal activity in the hippocampus was able to predict whether scents were correctly identified. Only nerve cells in the amygdala, a region involved in emotional processing, reacted differently depending on whether a scent was perceived as pleasant or unpleasant.

Nerve cells react to the smell, image and name of the banana

In a next step, the researchers investigated the connection between the perception of scents and images. To do this, they presented the participants in the Bonn study with the matching images for each odor, for example, the scent and later a photo of a banana, and examined the reaction of the neurons. Surprisingly, nerve cells in the primary olfactory cortex responded not only to scents, but also to images.

"This suggests that the task of the human olfactory cortex goes far beyond the pure perception of odors," says co-corresponding author Prof. Marc Spehr from the Institute of Biology II at RWTH Aachen University.

The researchers discovered individual nerve cells that reacted specifically to the smell, the image and the written word of—for example—the banana. This discovery indicates that semantic information are processed early on in human olfactory processing. The results not only confirm decades of animal studies, but also show how different brain regions are involved in specific human odor processing functions.

"This is an important contribution on the way to decoding the human olfactory code," says Prof. Mormann. "Further research in this area is necessary in order to one day develop olfactory aids that we can use in everyday life as naturally as glasses or hearing aids."

More information: Marcel S. Kehl et al, Single-neuron representations of odours in the human brain, *Nature* (2024). DOI: 10.1038/s41586-024-08016-5

Provided by University Hospital of Bonn

How a medtech market opportunity is shaping up for wearable neurotech

When you think of brain stimulating medtech, startups building wearables as therapeutics probably aren't the first thing that springs to mind. Such tech is still flying fairly under the radar — perhaps, in part, because these sorts of companies have raised a fraction of the investment that's been ploughed into invasive technologies for targeting treatments at the human brain.

This medtech startup, which was founded back in 2013, has raised a total of $30.4 million to date to fund development of its wearable brain-stimulating technologies targeting a range of mental health and metabolic conditions. It has said it's aiming to close a Series B by the end of the year, too – which could add another $40M to that pot.

But the amounts involved — still in the tens of millions — look modest compared to the costs of commercializing invasive neurotech. Or the billions that can be required to develop new pharmaceuticals. Which is explains why Baldwin is so bullish on neurotech, dubbing it "a great place to invest".

A portfolio of treatment wearables

The scope of the market opportunity is another angle here that's exciting investors. There are many potential therapeutic applications for neurotech wearables – with depression just one of multiple conditions and diseases where devices makers claim they can make a difference.

It's also running U.S. clinical trials for separate wearables targeting PTSD and Type II diabetes — and the startup hopes to turn all these efforts into a pipeline of approvals over the next two years. Including another neurotech device that's focused on treating obesity risk and promoting weight loss by targeting biological mechanisms that store visceral fat.

Baldwin tells TechCrunch the deeptech fund was attracted to Neurovalens by "the sheer breadth of where this technology could be applied".

"In terms of how you can get to market in massive [healthcare] markets, once you're through all the clearance regulations… you can do this quite effectively," she explains, saying the relatively small capital outlay required to get to that point "made sense" for a deep tech, early stage investor.

She's also upbeat about where the neurotech market is headed – pointing to projections that brain-targeting medtech is poised for major growth over the next five years.

Currently, the market as a whole – factoring in both invasive and non-invasive neurotech – is worth around $13 billion-$14 billion, per Baldwin, but she flags forecasts predicting this will rise to $40 billion by 2030.

Image Credits: Bryce Durbin/TechCrunch

How much of that growing pie ends up going to invasive neurotech startups vs wearables remains to be seen. But it seems a fair bet that non-invasive approaches have a good chance of gaining ground quickly – since, once they have the necessary approvals, their kit can be prescribed earlier, thereby potentially reaching more patients.

When IQ was first considering a neurotech investment, Baldwin recounts how McKeown – who was a neuroscience professor at San Diego university at the time – had been exploring neurostimulation as a treatment for obesity.

"We're stimulating the same area in the brain that controls how your body manages energy," he explains, saying the startup has been able to show "really significant" reductions in visceral fat, i.e. fat that's stored around organs, elevating a person's health risks.

"One of the joys of being a deep tech investor is just sitting down with your founders and saying, yeah, what if?" Baldwin continues. "That was what was so particularly attractive to Neurovalens; that they were able to apply their technology to several massive, globally important themes, rather than just have to drill down into one."

IQ opted to make its neurotech investment in a startup developing wearable medtech, rather than something more invasive like brain implants – but Baldwin stresses they were looking at "bold treatments". Evidently, though, the complexity and cost involved in commercializing implanted neurotech tipped the scales in favor of a head-mounted route in.

"When you go invasive it's a whole different level of complexity," she emphasizes. "In terms of regulatory, the cash required to get there, the kind of team support you need – from not only the medical profession but also the regulatory profession. It's a very different investment."

A cost efficient, scalable market opportunity

What about market opportunity? Given how many conditions and diseases medtech neurotech builders are eyeing this could end up scaling considerably, too, in the coming years.

According to the CDC, the percentage of people in the U.S. aged 18 and above who report having "regular feelings of depression" stands at 5%. While data from the U.S. National Center for Health Statistics for 2015 to 2018 found that 13.2% of U.S. adults had used antidepressant medications over the past 30 days – with rates of medication for depression trending upwards since its last survey.

Anxiety is another target area for non-invasive neurotech – and the CDC records U.S. adults experiencing regular feelings of "worry, nervousness, or anxiety" as even greater: 12.5%.

Turning to sleep disorders, between 30%-40%+ of U.S. adults report getting insufficient sleep. Although rates of chronic insomnia specifically are lower: A recent survey commissioned by the American Academy of Sleep Medicine found

that 12% of U.S. adults had been diagnosed with this more disruptive sleep disorder.

Diabetes is another major problem, in the U.S. and globally – one which can have very serious health consequences. According to the Centers for Disease Control and Prevention (CDC) more than 38 million Americans have diabetes – around 1 in 10 of the population – and between 90% to 95% of those have Type II diabetes, aka the kind Neurovalens hopes to be able to treat with its neurotech wearable.

Obesity, which can lead to a person developing diabetes, is even more prevalent – with more than 2 in 5 adult Americans being obese, per the CDC.

Another of Neurovalens' target conditions — PTSD — is a lot rarer. But the National Center for PTSD, a division of the U.S. Department of Veteran Affairs, has suggested about six in every 100 people will experience it at some point in their lives. And while there's a strong association between PTSD and military service, McKeown highlights that a particularly high risk group are middle aged women who have suffered from domestic abuse.

He says the startup is particularly excited about the PTSD wearable in development as the condition is notoriously difficult to treat. "PTSD doesn't respond very well to drugs – there are no really approved treatments. So we might be the first treatment available," he suggests.

When its PTSD trial wraps up, giving them a chance to fully review the data, he says they may seek to submit that wearable under the FDA's Breakthrough Devices Program which can speed up the process of U.S. regulatory review. So McKeown says they're hopeful this medtech product – slated to be called Modius Spiro – could be approved as soon as next year.

Closer in line for clearance is Neurovalens' obesity device (aka the Modius Lean) — which they've been trialing for longer. McKeown says they're anticipating approval for that either later this year or early next. While the aforementioned diabetes device (Modius DM) is further out – but he says they hope to have FDA approval for it in 2026.

Neurovalens is also considering commercializing a wearable for depression — which, if it goes ahead, would be called the Modius Mood — but the startup has yet to decide on whether to take that forward.

While the commercialization of these higher risk category treatments must wait for a greenlight from the FDA before they can proceed, the medtech company does have two products approved already (for chronic insomnia and GAD). These therapeutic wearables will be launching in the U.S. in the next few months so it will be switching into active marketing soon.

These first, lower risk neurotech products offer a chance for Neurovalens to test how much appetite there is for wearable neurotech in healthcare.

Despite being based in and developing out of Europe, its go-to-market strategy has always been focused on going to the U.S. first. McKeown says the FDA represents the "gold standard" for medical device approval. It's also a required step to access the country's massive healthcare market.

While there's no guarantee the FDA will approve any of the startup's more novel (and higher risk category) treatments, McKeown is convinced the market opportunity it's been working towards for so long is poised for lift-off.

"There's so much research being carried out – even [implanted] devices are now slowly making their way through to get reimbursement in the U.S., under the MediCare or the private healthcare payers. So the opportunity in general is just really exploding."

He argues this is even more true of the non-invasive sector – pointing out these types of devices sit "quite close" to the consumer health category, where neurotech kit makers are bringing more devices to market that make (unregulated) wellness claims. "Although our devices are prescribed, they're prescribed at the really earliest stages," he emphasizes.

"An implanted device for, say, anxiety or a mental health issue is a last resort," he adds, whereas neurotech wearables — being totally non-invasive — have the potential to achieve much greater scale and patient impact.

Now for the challenges...

Still, even with close to a decade of development work clocked up by some neurotech startups the challenges of commercializing head-mounted brain-stimulators undoubtedly makes for a long list.

Discussing hurdles Neurovalens has had to negotiate to get this far McKeown talks unbroken for several minutes.

His list includes taking theoretical lab work and presenting it to investors to convince them to cut a check and take a bet it can be translated into clinically validated outcomes; convincing doctors to involved their patients in trials for novel and experimental treatments; and conducting clinical trials to amass data to make a convincing case for medical device regulators to approve novel treatments.

"We just focus on making patients better. So the challenge... is showing to the FDA how well we can do this, and [that] the safety profile and the risk profile is proportionate to that," he explains.

"And then the challenge after that is, well, how do you start selling it?"

Assuming an FDA greenlight, medtech players also need to tackle the issue of reimbursement — convincing healthcare payers the treatment represents value for money — if they want to get their kit into the hands of patients at major scale. And, if that goes well, they arrive at the next challenge: Patient education.

For neurotech, this means getting people to look beyond what are still rather whacky optics (brain zapping headbands) and see a wearable device as a viable treatment for, say, a mental health issue alongside more established choices like therapy and medication.

There's a further wrinkle where patients are concerned, too, as a positive outcome from neurostimulation as a treatment is not guaranteed.

As is often the case with all sorts of medical treatments, patient outcomes can vary. But there's perhaps a particular incongruity if a gadget is not doing what it's supposed to given consumers are so accustomed to having high tech utility on tap, thanks to the rise of smartphones or even consumer wearables.

Flow Neuroscience, the Swedish medtech we met in the first part of this series, has had to device a strategy to tackle the challenge of variable efficacy.

It's chosen to commercialize an electrical form of neurostimulation known as transcranial direct current stimulation (tDCS) for its first product, which is depression-treating wearable. However CEO and co-founder Erik Rehn accepts tDCS may not work for every person — but he's quick to point out that antidepressants and other drugs have the same issue: "With some people it works great, with others not."

"The reality of it is that people's brains are different, and also people's depression. Depression as a diagnosis is very heterogeneous," he tells TechCrunch. "It's a big problem, of course, but we're kind of stuck with the terminology… that's what treatments are approved for."

Medtech builders have two options, in Rehn's view. One: taking a "precision medicine" pathway that narrows and optimizes targeting – but also requires "advanced equipment" and techniques that may crimp accessibility and raise costs. Two: "Make something that's cheap and available to everyone, but it might not work for everyone – but everyone can try it." The second route is what Flow opted for.

This strategy shoots for greater scale, and in doing so — the idea is — there's a better chance of finding those patients who will respond well to the treatment. Crudely put, it could be described as spray and pray. (Or perhaps scale to prevail.) And, along the way, there will be some patients for whom the wearable therapeutic works as hoped and some who will be disappointed.

Rehn admits it would be "very interesting" to better understand and predict patient outcomes – and he says Flow has done research exploring why tDCS helps some people but not others. But moving too far in that direction this would shift the startup's strategy closer to the "precision medicine" approach he believes is too restrictive to build traction and scale.

How to maximize efficacy while also keeping neurotech cheap and convenient to use — while also building a viable business that can deliver returns to investors — is, he suggests, "an open question."

It's striking how different Neurovalens' approach is to this neurotech challenge of uncertain outcomes. It's opted for an R&D intensive strategy that has enabled it to develop a range of devices during a pre-market phase, each aimed at distinct and precisely defined conditions (and, therefore, patients).

"We really want to have a well defined patient that has the very specific disease that we treat," emphasizes McKeown.

This portfolio play allows the startup to tweak the neurostimulation dosage for each patient segment — a degree of targeting that should help it to mitigate uncertain outcomes. (So, for example, its wearable for treating anxiety is not just for anyone suffering anxiety but for the specific condition generalized anxiety disorder (GAD); similarly its insomnia device is not for any sleep disorder, just "chronic insomnia".)

It's fair to say this is not the typical startup approach as it involves years of preparatory way-paving before a budding business is even able to introduce its first products. Whereas Flow's B2C (and, later, it hopes B2B) route looks more a more familiar startup playbook.

Having multiple medtech products in development simultaneously obviously ramps up costs and demands on the team. It also requires a decent funding cushion to support years of R&D before the business is in a position to pull in meaningful revenue from device sales. This explains why Neurovalens has raised so much more (around 3x) investor cash vs Flow (the Swedish startup had raised a total of just over $11M back in 2021 when it bagged its $9M Series A so appears to have taken a far leaner approach to funding.)

"We have been doing R&D for a long, long time," McKeown admits. "It feels like forever."

How has the startup stuck at it for so long? "We were quite reserved in our milestones," he responds. "Every big milestone we hit ahead of time and ahead of budget gives investors confidence to keep reinvesting and to get to the next milestone." Whereas, he suggests, an excess of ambition can lead to investors jumping ship when unrealistic expectations are not met.

Neurovalens getting its first couple of FDA approvals – the first was for the insomnia wearable in fall last year – was a major credibility milestone, he adds.

“Now that we have got our first two approvals then there’s really no doubt in the investor’s mind that we can do this.”

Even with carefully curated patient segments, it’s clear Neurovalens’ neurostimulation won’t work for every brain it’s applied to. And, as we noted above, that’s a particularly interesting challenge for a hardware startup to grapple with. Patients have learned to expect patchy results from popping pills but when it comes to consumer tech expectations can be a lot more demanding of insta results.

“People assume that it’s a bit like an iPhone – that technology just works for everyone,” McKeown observes, yet ‘it just works’ is not the case with neurotech. “There’s a bit of an education piece.”

One future hope for further reducing variable outcomes from non-invasive neurostimulation is if device makers can find ways to better personalize the treatment per patient. But that’s something else startups in this space will have to scratch their heads over in the coming years.

Many scientists are neurodivergent. Architects are finally starting to build labs designed for them

Imagine the stereotypical biotech lab space: smudge-free counters and walls, blindingly white surfaces, and an array of stainless steel machines, all set up for maximum focus and cleanliness to further the pursuit of innovation. But a new study about the way different kinds of scientists use lab space suggest the one-size-fits-all approach isn’t just aesthetically sterile, it might actually inhibit scientific research, and require a new design approach to fix.

Roughly half of lab workers and scientists identify as neurodivergent, or somewhere on the autism spectrum (double the global average of 20%), according to new research conducted by Advanced Research Clusters (ARC), a

British developer of lab space, HOK, a global architecture practice and the University of the West of Scotland. The same survey found the rate of autism among lab workers is 25%, or 25 times the U.K. average.

That's an opportunity to rethink design and radically change how labs look and operate, says HOK principal Kay Sargent, the firm's director of thought leadership for interiors. The research found a gaping need for inclusive scientific spaces that holistically look at and rethink auditory, visual, and tactile elements to eliminate sources of disruption and disengagement.

In short, Sargent says, traditional lab design raise a key question: "Are you eliminating the potential for people who are really going to be game changers to be successful?"

They're not expensive changes, and don't really add much to the project budget, says Sargent. But they are thoughtful touches that can significantly improve productivity.

HOK has been studying the wider issue of design for neurodivergent populations for roughly a decade, motivated by the general lack of research on the topic. "There was a real drought of information, almost a total vacuum on how to design the built environment for sensory processing," she says. "We believe really strongly that the environments that we're designing will have an impact on the people in them, which can be good and bad."

Roughly 18 months ago, ARC asked HOK to look into this issue as it impacts lab users, since they were fielding more requests for incubator space for small startups and wanted to improve the types of labs they were building.

A lack of sensory diversity can lead to reduced productivity, poor recall, burnout, stress, and recruitment and retention challenges. The downsides of business-as-usual facilities rarely gets addressed by workers, especially junior staff; just 30% of younger innovators consider themselves neurotypical, the study found.

"Often, neurodivergent employees will manage their work environments by hiding signs of their neurodiversity," says Dr. Edward Edgerton, a University of West of Scotland, who participated in the research. "However, even when their neurodiversity is recognized, their workplaces can still be exhausting, impacting

negatively on their performance and well-being. Few organizations have considered neurodiversity workspace design, particularly for laboratories."

Life science real estate boomed in the early part of the pandemic, creating an arms race in terms of high-end amenities, outdoor space, and terraces and balconies. But Sargent says that amenity spending, and more comfortable dining and social spaces, doesn't really solve the distraction problem for workers who spend their entire day within the research and work space. The goal was to create a more human experience for those within wet labs and scientific workspaces.

The solution, according to the research, is to create labs that include biophilia and a variety of workspace options; the layout caters to different levels of sensory input, not "one size misfits all," as Sargent explains. The focus is on focus itself. The proposed design offers ways to cut down on different types of overstimulation and eliminate the impact of noisy equipment, while also providing more daylight, natural elements, and more choice.

That means bright colored walls to reduce the sterility of labs, but also nooks and crannies with less visual and auditory stimulation for private work. Meeting rooms should have flexible seating that allow for sitting and standing, as opposed to huddling around one large rectangular table. They also recommend reducing sharp edges, plastic and metallic materials, and see-through walls with more private labs and organic materials and shapes.

Rethinking the lab layout

Biology labs tend to cram in workers due to the financial considerations of real estate development; life sciences space costs multiples more than traditional office space. That tends to result in open, contiguous lab space, with regular rows of work benches, cellular support labs for imaging and tissue cultures on the ends, and a small amount of breakout space on the periphery.

HOK's solution is a lab neighborhood, featuring a variety of neurozones meant to break up the floor plan and the workday. A mock 100-person lab prototype included in the report is subdivided into two wings, with a central bay that include congregate and creative space for collaboration. Commune modes of

space, more akin to the standard layout, are next to the central bay to maintain financially required density, but sport a wider range of seating, benching, and furniture options.

Further out from the core, a number of differentiated spaces offer more varied, inclusive environments: a series of biophilic terrariums break up repetitious seating and views to create quiet space for hypersensitive researchers; contemplative pods offer spaces for group meetings and work; quieter commune spaces on the edges include more acoustic absorption and organic furniture and bench seating. In addition, the transparent barrier between lab areas would be replaced with fully glazed partitions to add visual privacy. This layout better integrates spaces for rest and relaxation amid work areas, and eliminates corner offices for executives, providing additional opportunity for needed shared space.

Sargent believes this kind of design approach offers the same benefits as universal design, which views architecture that make it easier for those with mobility, visual, and other disabilities to navigate a space as having society-wide accessibility benefits. HOK is actually doing a tracking study in one of its own offices, testing the impacts of this kind of design approach, and will continue to study the impacts of its newer spaces, which will utilize a similar approach to user diversity.

“I know no one who isn’t impacted by sound, color, temperature, or texture,” she says. “But what might be annoying for someone who’s neurotypical can be debilitating for someone that’s neurodivergent. They tend to be that canary in the coal mine, and they’re going to feel it first, and they’re going to feel it more intensely. But it doesn’t mean that it’s not impacting every other person in a space.”

A neuroscientist is more efficient than ever after making 3 simple changes that take advantage of when her brain works best

- A 9-to-5 working day can block creativity and deep focus, a neuroscientist said.
- The brain is primed to do certain types of work at certain times of day, according to Mithu Storoni.
- Storoni shared three things she does to work more efficiently than ever before.

Mithu Storoni, a neuroscientist and expert on mental stress, made three "radical" changes to the way she works after writing her latest book on optimizing workflow.

While researching "Hyperefficient," a book about working efficiently in the age of AI, she realized the traditional 9-to-5 pattern of office work blocks creativity and doesn't take into account the natural rhythm of the brain or a person's individual needs, Storoni told Business Insider.

Data suggests the brain is better at performing certain tasks at certain times of the day, Storoni said. Creative, innovative problem-solving and thinking "peaks off-peak" early in the morning and late at night, Storoni said. In the mid to late morning, we tend to be more alert and able to do tasks that require deep focus, whereas, after lunch, it's common to have an energy slump.

Most jobs will have an employee doing different types of work, from idea generation to admin, and each type requires a different mental state, she said. This means a rigid working schedule is ultimately inefficient.

"If you impose the same routine on everyone, you are actually preventing people from working at their best at what they're doing," Storoni said. "We need to radically rethink the way we work."

There's evidence to suggest that flexibility leads to a more productive workforce. In the 2023 Future Forum Pulse survey — which is backed by Slack and collected data from 10,646

knowledge workers across the US, Australia, France, Germany, Japan, and the UK — 39% of people with full schedule flexibility reported higher productivity scores than those who had no control over their hours.

In the book, Storoni outlines the three "gears" of the brain: with gear one being a daydreaming, relaxed state, gear two being the sweet spot for focus, and gear three being a hyperaroused, stressed mode. She shared the measures she takes to keep herself in gear two when working.

She stressed that this isn't about "hacking the system" in an attempt to be as consistent as a computer or force your brain to work in a certain way, but rather encouraging the brain to work the way it wants to work.

Schedule tasks around brain rhythm

As much as possible, Storoni now schedules her working day around the type of tasks she needs to do. "I work according to the time of day," she said.

Typically, she starts her day with a workout, but if she needs to do something creative, like write a piece for a magazine, she'll block off that time for work and find another time to exercise.

Storoni is mainly freelance, which gives her more flexibility than a salaried employee. But provided you have at least some agency over when you do which tasks, this idea could be applied to a typical working day, she said.

She does something creative when she has a mental block

When Storoni hits a wall, she leaves her desk and does something creative. "Even if it's not actually working on that creative problem, I do something parallel that's creative," she said. It helps stimulate her imagination and get the juices flowing.

Taking a break to do something creative can help with writer's block. Daniel de la Hoz/Getty Images© Daniel de la Hoz/Getty Images

This could be reading some fiction, listening to an audiobook on a walk, or even something more active like painting or drawing. "That puts me into the right state of mind for when I come back and overcome that mental block," she said.

Taking time away from the screen is essential and doesn't necessarily mean you have stopped working. "I go for a walk confident that actually, even though I'm not visually sitting and looking like someone who's working, I know my mind is working," she said.

This attitude helps her take breaks without feeling guilty or unproductive.

Shut off all potential avenues of incoming information

Maintaining a state of focus (gear two) can be hard and requires an element of self-control, Storoni said, so minimizing distractions can be very helpful.

When she's doing focused or creative work, Storoni puts her phone face down on silent, pauses her email notifications, and doesn't read anything.

"I don't speak to anyone, I don't take any messages, nothing until I'm out of that zone," she said, adding: "As soon as you engage with something, you can't say, 'okay, we're not processing this information.' You have to because that's what attention is."

Having to process information from different streams at once can easily tip someone out of that focused zone as there's too much competition for their attention. This means there are fewer resources for the task at hand, and the quality lessens, she said.

Singling out distinct brain regions and mechanisms involved in our ability to pay attention

TMS (delivered via magnetic coil, left) and tACS (represented as sinusoidal waves, right) are non-invasive techniques used to modulate and study human brain activity. Credit: Ankita Sengupta

The human brain is a complex organ with over 80 billion neurons. But it can still trip up when it comes to multitasking. Trying to send an email at the same time as talking to someone can almost be enough to short-circuit our synapses, leaving us distracted and prone to making mistakes.

"The brain is a very large, complex, connected network, but even with simple things, bottlenecks happen. It's very hard to do two unpracticed actions at the same time," explains Sridharan Devarajan, Associate Professor at the Centre for Neuroscience, Indian Institute of Science (IISc).

Sridharan has long been fascinated by attention—how our brain decides to focus on one specific object in front of us and not get distracted by other objects in the background. In two recent studies, his team has teased out distinct brain regions and mechanisms involved in our ability to pay attention. Such insights can help scientists better understand and treat attention-related brain disorders.

Until recently, scientists assumed that attention was a unitary phenomenon. However research in Sridharan's lab and others has shown that this is not the case—we now know that there are at least two components or parts of attention that can be quantified, called sensitivity and bias.

"When you pay attention to something, the brain processes information from it better and extracts useful content from that information—this aspect of attention is what we call sensitivity," explains Sridharan. "Bias is the brain deciding that some information is more important than others for making decisions."

Imagine driving a car down a busy road (which is almost everywhere in Bengaluru). Your eyes may spot many different objects, bombarding your brain with myriad visual sensory inputs. But your brain chooses to focus on the car right in front of you. Therefore, it keenly tracks this car to pick out its every movement—this is sensitivity. Simultaneously, your brain decides that cars on the other lane are not important for your decision-making and selectively filters out information from them—this is bias.

In a recent paper published in *Nature Communications*, Sridharan and his group have shown that a particular region of the brain, called the right posterior parietal cortex (rPCC), specifically regulates the bias component of attention. They zeroed in on rPCC because clinical studies had shown that patients who suffered a stroke in this region completely neglected objects on one side of their visual world.

The group asked human participants to covertly view two objects on different sides of the screen, but attend to one of the sides indicated by a visual cue. Depending on how accurately and reliably the participants were able to make out

the object's features on the cued versus the uncued side, the researchers were able to quantify sensitivity and bias independently for each.

"A challenging aspect [of the project] was recruiting participants as volunteers," says Ankita Sengupta, Ph.D. student in Sridharan's group and the lead author of the study. "There is a gap in the understanding of safety of neurostimulation techniques; we need to educate the general public about this."

The team used non-invasive techniques called transcranial magnetic stimulation (TMS) and transcranial alternating current stimulation (tACS) to briefly disrupt brain activity in the participants' rPCC. What they saw was that disrupting rPCC temporarily diminished the bias component in the participants.

In another paper in *eLife*, Sridharan's team also tracked electrical activity ("neural signatures") related to sensitivity and bias independently, using electroencephalograms (EEGs) recorded non-invasively from participants' brains.

The researchers started out by trying to understand whether bias or sensitivity plays a major role during something called the "attentional blink"—when our brain is unable to process the second of two objects that it must track in rapid succession.

"If you ask people to pay attention to a rapid stream of information and present them with multiple target objects that need to be attended to, when the first target comes up, they will register it. But if the second target comes up very soon after the first target, they will likely miss it," explains Sridharan.

"It's just like your eyes blinking. It is almost as if the attentional system—once it receives a piece of information—blinks, and so the next piece of information cannot get in if it comes in too soon [after the first]."

The participants in this case were presented with black and white gratings tilted in different directions, one after the other. They then had to push buttons to answer questions about how these targets were tilted, all while their brain's electrical activity was being recorded. The researchers analyzed how well the participants were able to distinguish the second target that they were presented with. With the help of computational models, the team was able to tease apart the roles of sensitivity and bias during the attentional blink.

"Initially, we expected both components of attention—sensitivity and bias—to be impaired," says Swagata Haldar, Ph.D. student working in Sridharan's lab and lead author of the *eLife* study. "To our surprise, we found that attentional blink affects mainly sensitivity, and not bias."

Sridharan believes that understanding such phenomena can eventually help us treat attention disorders with more precision. Current treatments involve the use of strong medicines or drugs that can lead to abuse and side-effects.

"If you really want to treat attention disorders, it could be risky to give psychostimulant drugs that will affect everything at the systemic level," he says. "You have to know the pathways involved, the different components and pieces, and how the brain puts them together to create this phenomenon called attention. Then you can provide much more targeted treatments."

More information: Ankita Sengupta et al, The right posterior parietal cortex mediates spatial reorienting of attentional choice bias, *Nature Communications* (2024). DOI: 10.1038/s41467-024-51283-z

Swagata Halder et al, Distinct neural bases of subcomponents of the attentional blink, *eLife* (2024). DOI: 10.7554/eLife.97098.1

Provided by Indian Institute of Science

Neuroscientists discover two specific brain differences linked to how brains respond during tasks

A new study by neuroscientists at Florida State University has revealed brain differences that may explain why humans demonstrate a variety of cognitive abilities and behaviors.

The research, conducted by a multi-institution team led by FSU Associate Professor of Psychology and Neuroscience Caterina Gratton and research technician Ally Dworetsky, shows that two forms of individual differences may

predict cognitive abilities, explain behavioral differences and even pinpoint biomarkers of brain disease.

"We discovered that in addition to individual brain differences located along the borders of brain regions, such as the border between visual and parietal regions of the brain, individual differences can also occur in a different way. Some variations are further away from where you would expect, popping up like islands," said Dworetsky, a research assistant in the Gratton Lab and the study's lead author. "We call these ectopic intrusions since they occur in unexpected locations."

The study, in coordination with colleagues at Washington University in St. Louis, Johns Hopkins School of Medicine, University of Oxford and the University of Nebraska-Lincoln, is published in the journal *Nature Neuroscience*.

"This research reconceptualizes how we think about how brains can differ from one another and what these differences mean," Gratton said. "Additionally, this helps us approach new research questions such as how these differences affect brain development, behavioral traits, the development of disorders and more."

With a more complete understanding of what is happening in the brain, researchers can better assess the mechanisms underlying what leads brains to differ from one another, which supports the study of brain disorders and diseases such as Parkinson's disease, an area of research that Gratton has pursued for years.

"This collaboration is a continuation of a previous study on trait-like variants in human functional brain networks that was published in the *Proceedings of the National Academy of Sciences* in 2019," Dworetsky said. "The goal of these studies is to better understand how individual differences in the brain manifest in people and reconceptualize how variability in the brain may link to differences in cognition and behavior."

This recent study, titled "Two common and distinct forms of variation in human functional brain networks," is unique in how it approaches brain network variations, because previous work on this topic treated individual differences as equivalent and primarily linked to boundary shifts between the borders of brain regions. Identifying additional individual differences in the form of ectopic

intrusions helps researchers better understand how each of these differences manifests and how the brain functions normally.

By taking extensive measures of individuals, including scanning the brains of individuals 10 or more times using functional MRI scanning, researchers can reliably identify these locations and obtain more detailed characterizations relative to what is possible with more typical approaches. This data was used to develop methods that identify the border shifts and ectopic intrusions.

"What we found when looking at the data is that the ectopic variants are a quite common phenomenon—it's more frequent than we expected to have these unusual locations of variations," Gratton said. "This means we need to think about mechanisms for how the brain can differ that may cause long-range changes in both the connectivity and function between different brain regions."

Dworetsky, who earned her bachelor's degree in 2018 from Washington University in St. Louis and joined the Gratton Lab in 2020, worked to show that both border shifts and ectopic variants also differ in many ways: they are located in different parts of the brain, they interconnect with different brain systems, and they differ across samples that are genetically similar.

"We learned that separating border shifts and ectopic intrusions can be very informative in our understanding of how these individual differences occur in our brain and also what they may tell us about how the brain functions," Dworetsky said.

With team members from collaborating institutions specializing in various analyses, ranging from using machine learning techniques to predict demographic and behavioral variables from brain data to heritability and genetic analysis, the researchers were able to better understand genetic and environmental factors and how they played out in the manifesting of brain differences.

"We plan to dig into the cognitive variables that we predict will be affected by these differences, especially to see if these differences can be predictive in certain brain disorders," Gratton said of forward-looking research.

More information: Ally Dworetsky et al, Two common and distinct forms of variation in human functional brain networks, *Nature Neuroscience* (2024). DOI: 10.1038/s41593-024-01618-2

Provided by Florida State University

New class of drugs target brain metabolism to treat Alzheimer's patients

Recent research highlights the potential of targeting the brain's metabolism to treat Alzheimer's disease, a condition that disrupts cognitive functions like memory and thinking.

Scientists from Stanford's Knight Initiative for Brain Resilience, along with collaborators from institutions like the Salk Institute and Penn State University, have been investigating how to restore healthy brain function by focusing on the kynurenine pathway, a key regulator of brain metabolism.

The brain's metabolism relies on glucose, the fuel that powers neurons, which are crucial for thought and memory. Alzheimer's disease interferes with this process, causing a steady decline in cognitive abilities.

The scientists hypothesize that the kynurenine pathway becomes overactivated as amyloid plaque and tau proteins—both hallmarks of Alzheimer's—build up in the brain. These proteins, believed to be key contributors to the disease, may trigger metabolic disruptions that harm the neurons' ability to communicate.

The breakthrough came when the research team discovered that blocking the kynurenine pathway in mice could improve cognitive function and memory. The scientists found that drugs targeting the kynurenine pathway helped restore the balance of the brain's metabolism and improved behavior in mice engineered to develop Alzheimer's-like symptoms.

Lead author Katrin Andreasson, a neurologist at Stanford University, explained, "We were surprised that these metabolic improvements were so effective at not just preserving healthy synapses but in actually rescuing behavior. The mice

performed better in cognitive and memory tests when we gave them drugs that block the kynurenine pathway."

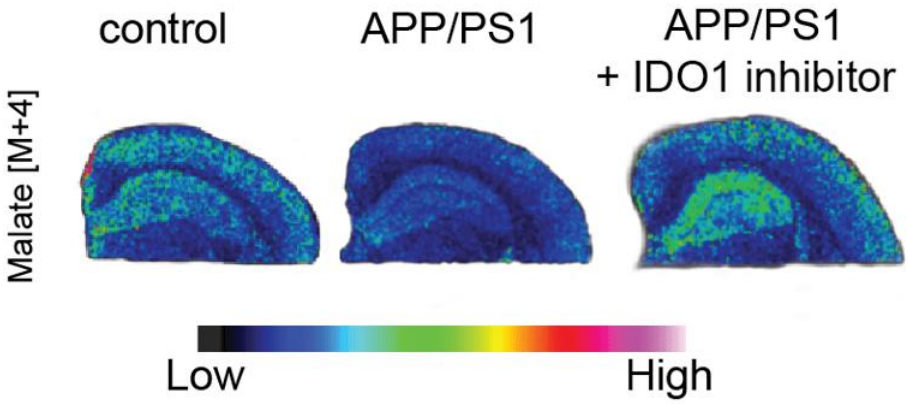
Related Stories

How does the brain make memories? Can ultrasound help treat Alzheimer's, Dementia and the brain? Physical activity may protect your brain as you age

The study, published in the journal Science, represents a collaboration across several top research institutions. The kynurenine pathway plays a crucial role in producing lactate, an energy molecule essential for neurons to function properly and maintain the connections, or synapses, that allow brain cells to communicate. Andreasson's team focused on an enzyme called indoleamine-2,3-dioxygenase 1, or IDO1.

This enzyme generates kynurenine, and the researchers suspect that amyloid plaques and tau proteins overstimulate IDO1, leading to an overproduction of kynurenine. This disrupts the ability of astrocytes, the brain cells that support neurons, to supply lactate, which in turn affects brain metabolism and damages synapses.

Astrocytes, critical cells that normally support brain function, can't produce sufficient lactate when the kynurenine pathway is overactive. Blocking the production of kynurenine in the laboratory experiments, however, restored the ability of astrocytes to provide energy to neurons, which helped stabilize brain function.

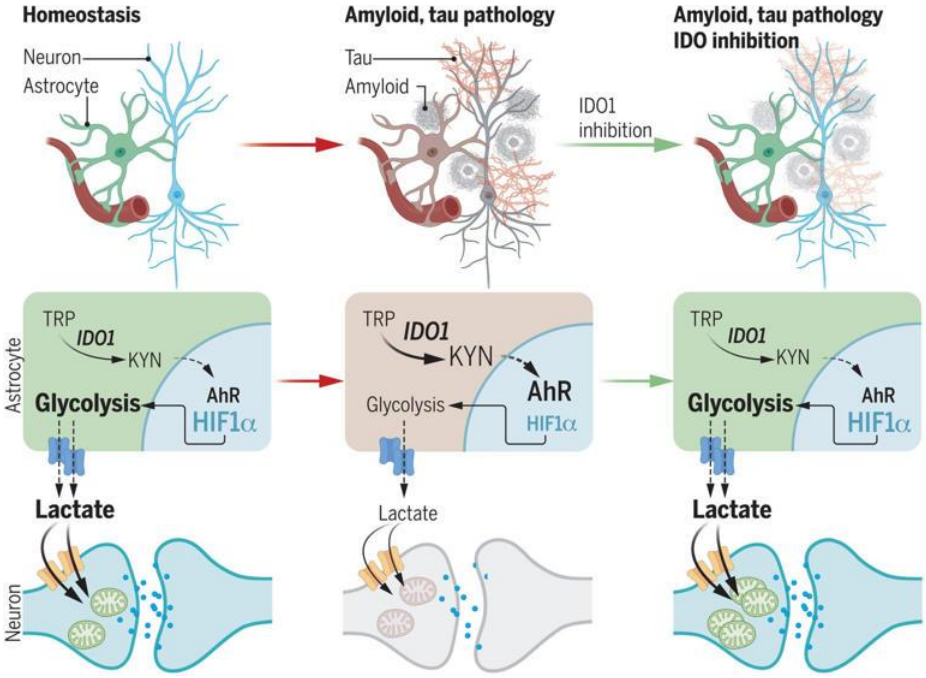


Researchers showed that mice with a genetic model of Alzheimer's disease lose glucose metabolism in the memory region of the hippocampus (center: 'APP/PS1' vs left: 'control'), but IDO1 inhibitor drugs restore normal metabolic levels (right: 'APP/PS1 + IDO1 inhibitor'). (CREDIT: Minhas et al, Nature (2024))© The Brighter Side of News

"The kynurenine pathway is overactivated in astrocytes, a critical cell type that metabolically supports neurons," Andreasson noted. She added that when this pathway is disrupted, it results in damage to synapses and hampers cognitive abilities, a key issue in Alzheimer's patients.

What makes these findings particularly promising is that drugs targeting the kynurenine pathway, specifically IDO1 inhibitors, are already in development for cancer treatments. These drugs, originally designed for oncology, can now potentially be repurposed for treating Alzheimer's.

This offers a significant advantage in speeding up the process of testing these therapies in humans. "Best of all," said Andreasson, "IDO1 is well known in oncology, and there are already drugs in clinical trials to suppress IDO1 activity and production of kynurenine."



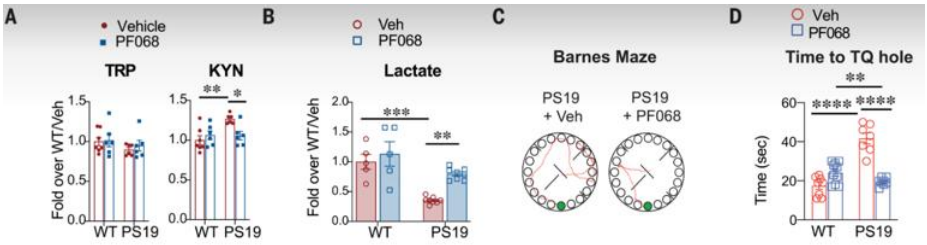
Mechanism of action of astrocytic IDO1 activity across AD pathologies. Astrocytes (in green) generate lactate, and glycolytic gene expression is partly regulated by hypoxia-inducible factor 1-α (HIF1α). (CREDIT: Science)© The Brighter Side of News

This ability to skip the lengthy process of developing new drugs from scratch could accelerate the time it takes to bring an effective Alzheimer's treatment to market.

Andreasson's team began testing the drugs in mice almost immediately, where they found that the intervention improved glucose metabolism in the

hippocampus—a region critical for memory—and enhanced the performance of astrocytes. The mice were able to better navigate obstacle courses designed to assess spatial memory and cognition after receiving the IDO1-blocking drugs.

One of the most exciting aspects of this research is that these improvements in cognitive function were observed in mice that modeled both amyloid and tau protein pathologies, which are the two primary features of Alzheimer's disease. "We also can't overlook the fact that we saw this improvement in brain plasticity in mice with both amyloid and tau models. These are completely different pathologies, and the drugs appear to work for both," Andreasson emphasized.



IDO1 inhibition rescues hippocampal memory and plasticity in mutant Tau PS19 mice. (CREDIT: Science)© The Brighter Side of News

Looking ahead, there is great optimism that IDO1 inhibitors could be tested in human clinical trials for Alzheimer's disease, with hopes of replicating the same cognitive improvements seen in lab animals. While earlier trials with these inhibitors focused on cancer outcomes, they did not track improvements in cognition or memory. Now, the research team is eager to apply these findings to Alzheimer's patients.

Andreasson and her colleagues hope to initiate human trials to evaluate whether the same benefits can be observed in people with Alzheimer's disease. If successful, this could be a game changer in Alzheimer's treatment, leveraging existing drugs and therapies from the cancer field to help combat one of the most challenging neurodegenerative disorders.

Study reveals a universal pattern of brain wave frequencies across mammalian species

Throughout the brain's cortex, neurons are arranged in six distinctive layers, which can be readily seen with a microscope. A team of MIT neuroscientists has now found that these layers also show distinct patterns of electrical activity, which are consistent over many brain regions and across several animal species, including humans.

The researchers found that in the topmost layers, neuron activity is dominated by rapid oscillations known as gamma waves. In the deeper layers, slower oscillations called alpha and beta waves predominate. The universality of these patterns suggests that these oscillations are likely playing an important role across the brain, the researchers say.

The work is published in *Nature Neuroscience*.

"When you see something that consistent and ubiquitous across cortex, it's playing a very fundamental role in what the cortex does," says Earl Miller, the Picower Professor of Neuroscience, a member of MIT's Picower Institute for Learning and Memory, and one of the senior authors of the new study.

Imbalances in how these oscillations interact with each other may be involved in brain disorders such as attention deficit hyperactivity disorder, the researchers say.

"Overly synchronous neural activity is known to play a role in epilepsy, and now we suspect that different pathologies of synchrony may contribute to many brain disorders, including disorders of perception, attention, memory, and motor control. In an orchestra, one instrument played out of synchrony with the rest can disrupt the coherence of the entire piece of music," says Robert Desimone, director of MIT's McGovern Institute for Brain Research and one of the senior authors of the study.

André Bastos, an assistant professor of psychology at Vanderbilt University, is also a senior author of the paper. The lead authors are MIT research scientist Diego Mendoza-Halliday and MIT postdoc Alex Major.

Layers of activity

The human brain contains billions of neurons, each of which has its own electrical firing patterns. Together, groups of neurons with similar patterns generate oscillations of electrical activity, or brain waves, which can have different frequencies. Miller's lab has previously shown that high-frequency gamma rhythms are associated with encoding and retrieving sensory information, while low-frequency beta rhythms act as a control mechanism that determines which information is read out from working memory.

His lab has also found that in certain parts of the prefrontal cortex, different brain layers show distinctive patterns of oscillation: faster oscillation at the surface and slower oscillation in the deep layers. One study, led by Bastos when he was a postdoc in Miller's lab, showed that as animals performed working memory tasks, lower-frequency rhythms generated in deeper layers regulated the higher-frequency gamma rhythms generated in the superficial layers.

In addition to working memory, the brain's cortex also is the seat of thought, planning, and high-level processing of emotion and sensory information. Throughout the regions involved in these functions, neurons are arranged in six layers, and each layer has its own distinctive combination of cell types and connections with other brain areas.

"The cortex is organized anatomically into six layers, no matter whether you look at mice or humans or any mammalian species, and this pattern is present in all cortical areas within each species," Mendoza-Halliday says. "Unfortunately, a lot of studies of brain activity have been ignoring those layers because when you record the activity of neurons, it's been difficult to understand where they are in the context of those layers."

In the new paper, the researchers wanted to explore whether the layered oscillation pattern they had seen in the prefrontal cortex is more widespread, occurring across different parts of the cortex and across species.

Using a combination of data acquired in Miller's lab, Desimone's lab, and labs from collaborators at Vanderbilt, the Netherlands Institute for Neuroscience, and the University of Western Ontario, the researchers were able to analyze 14

different areas of the cortex, from four mammalian species. This data included recordings of electrical activity from three human patients who had electrodes inserted in the brain as part of a surgical procedure they were undergoing.

Recording from individual cortical layers has been difficult in the past, because each layer is less than a millimeter thick, so it's hard to know which layer an electrode is recording from. For this study, electrical activity was recorded using special electrodes that record from all of the layers at once, then feed the data into a new computational algorithm the authors designed, termed FLIP (frequency-based layer identification procedure). This algorithm can determine which layer each signal came from.

"More recent technology allows recording of all layers of cortex simultaneously. This paints a broader perspective of microcircuitry and allowed us to observe this layered pattern," Major says. "This work is exciting because it is both informative of a fundamental microcircuit pattern and provides a robust new technique for studying the brain. It doesn't matter if the brain is performing a task or at rest and can be observed in as little as five to 10 seconds."

Across all species, in each region studied, the researchers found the same layered activity pattern.

"We did a mass analysis of all the data to see if we could find the same pattern in all areas of the cortex, and voilà, it was everywhere. That was a real indication that what had previously been seen in a couple of areas was representing a fundamental mechanism across the cortex," Mendoza-Halliday says.

Maintaining balance

The findings support a model that Miller's lab has previously put forth, which proposes that the brain's spatial organization helps it to incorporate new information, which carried by high-frequency oscillations, into existing memories and brain processes, which are maintained by low-frequency oscillations. As information passes from layer to layer, input can be incorporated as needed to help the brain perform particular tasks such as baking a new cookie recipe or remembering a phone number.

"The consequence of a laminar separation of these frequencies, as we observed, may be to allow superficial layers to represent external sensory information with faster frequencies, and for deep layers to represent internal cognitive states with slower frequencies," Bastos says. "The high-level implication is that the cortex has multiple mechanisms involving both anatomy and oscillations to separate 'external' from 'internal' information."

Under this theory, imbalances between high- and low-frequency oscillations can lead to either attention deficits such as ADHD, when the higher frequencies dominate and too much sensory information gets in, or delusional disorders such as schizophrenia, when the low frequency oscillations are too strong and not enough sensory information gets in.

"The proper balance between the top-down control signals and the bottom-up sensory signals is important for everything the cortex does," Miller says. "When the balance goes awry, you get a wide variety of neuropsychiatric disorders."

The researchers are now exploring whether measuring these oscillations could help to diagnose these types of disorders. They are also investigating whether rebalancing the oscillations could alter behavior—an approach that could one day be used to treat attention deficits or other neurological disorders, the researchers say.

The researchers also hope to work with other labs to characterize the layered oscillation patterns in more detail across different brain regions.

"Our hope is that with enough of that standardized reporting, we will start to see common patterns of activity across different areas or functions that might reveal a common mechanism for computation that can be used for motor outputs, for vision, for memory and attention, et cetera," Mendoza-Halliday says.

More information: A ubiquitous spectrolaminar motif of local field potential power across the primate cortex, *Nature Neuroscience* (2024). DOI: 10.1038/s41593-023-01554-7. www.nature.com/articles/s41593-023-01554-7

Your gut microbiome is more important than you think and it affects the brain

Even if you already think it's really important, it's *probably* even more important than you think it is. A study in mice found that the state of a mother's gut microbiome influences brain development in its young. In the case of lab mice, at least, the presence or absence of a particular bacterium during pregnancy can have serious knock-on effects.

In the human world, scientists have concluded that promoting a healthy gut microbiome will be fundamental to achieving long-term space missions. We've evolved to live on Earth, so staying healthy *off* Earth requires some delicate management. If you've tried to get to the bottom of how it's all formed and maintained by watching needlessly complex gut microbiome videos online, we get you. Hopefully, this particular piece of research-based news will strike a chord!

A pregnant mother's gut microbiome influences brain development in the fetus

In mice, at least.

A recent study at the University of Cambridge in the UK found that the presence of the bacteria *Bifidobacterium breve* in a pregnant mouse's gut supports the healthy brain development of the fetus it carries.

Cell processes relating to growth saw positive changes among the pregnant mothers who were given the bacteria. Meanwhile, nutrient transport to the brain increased.

What the study suggests is that it's possible to improve fetal development, specifically brain metabolism, by taking supplements of the *Bifidobacterium breve* bacteria.

It occurs naturally in a human's gut, but it's also available as a dietary supplement in probiotic drinks and tablets. Abbreviated to B breve, it lives in the intestines and produces lactic and acetic acid in the gut.

WebMD adds that it can "help break down food, absorb nutrients, and fight off 'bad' organisms that might cause diseases." It's commonly found in the gut of breastfed infants – one reason why breastfeeding trumps formula milk.

Giving mothers 'good' bacteria can help fetuses develop and grow in a healthy way

Even if a pregnant woman is malnourished, taking specific dietary supplements could help the development of the fetus she's nurturing, the study suggests.

Dr Jorge Lopez-Tello, the report's first author and a member of Cambridge University's Trophoblast Research Center, told Science Daily: "Our study suggests that by providing 'good bacteria' to the mother we could improve the growth and development of her baby while she's pregnant."

Treatments for when fetuses don't grow properly could focus on "altering the gut microbiome through probiotics," instead of offering "pharmaceutical treatments – with the risk of side effects – to pregnant women."

However, it's important to stress that it's impossible to predict exactly how studies like this will translate to humans. Nevertheless, one of the academics involved in the research described it as "exciting."

It "may pave the way" for future studies into the role of a mother's microbiome in the brain (or indeed general) development of the fetus. So, stay tuned!

Revolutionizing Neuroprosthetics Through AI-Driven Brain-Computer Interfaces: New Frontiers Unlocked by Dr. Pulicharla

he integration of Artificial Intelligence (AI) with neuroprosthetics is opening new horizons in the world of Brain-Computer Interfaces (BCIs). This innovative approach is transforming the way we understand human cognition and interaction with external devices, especially for individuals with neurological conditions. Dr. Mohan Raja Pulicharla's recent research, *"**AI-powered Neuroprosthetics for Brain-Computer Interfaces (BCIs)**,"* delves deep into this cutting-edge technology, exploring its potential and future implications.

What Are Brain-Computer Interfaces (BCIs)?

BCIs are systems that allow direct communication between the brain and external devices, enabling individuals to control machines or computers using their thoughts. Historically, BCIs have been an experimental technology used primarily in research settings. However, the advent of AI has propelled their development, allowing for more precise, adaptable, and efficient systems.

Applications and Future Impact

Dr. Pulicharla's study outlines several promising applications of AI-powered BCIs, particularly in medical settings. For instance, individuals with spinal cord injuries or neurodegenerative diseases can regain motor function through the use of neuroprosthetics controlled by BCIs. AI-powered systems can also assist stroke survivors in recovering speech or motor abilities by bypassing damaged neural pathways and directly connecting the brain to assistive devices.

Beyond medical applications, this technology has the potential to revolutionize various industries. Imagine hands-free control of machinery, computers, or even vehicles, driven purely by thought. AI-powered BCIs could also serve as communication tools for individuals with severe disabilities, offering them a newfound sense of independence and control over their environment.

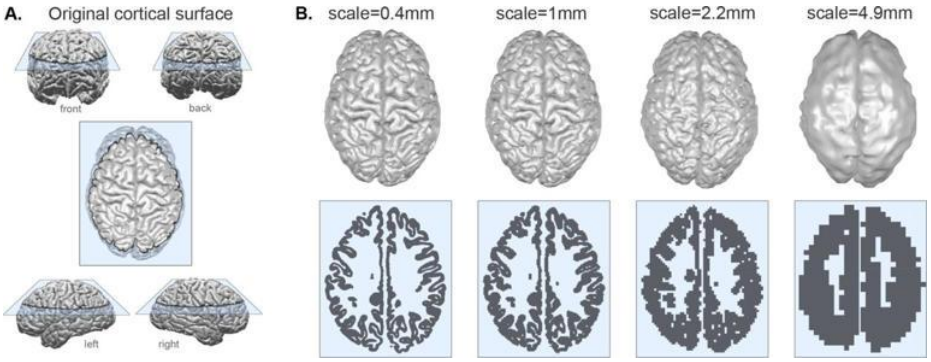
The Future of Human-Machine Integration

As highlighted in Dr. Pulicharla's research, the fusion of AI with BCIs and neuroprosthetics is still in its early stages, but the trajectory of this technology is

clear. The enhanced capabilities provided by AI will allow BCIs to evolve from experimental setups to widely available tools with broad applications. The continuous development of AI algorithms, coupled with advancements in neuroprosthetic devices, will drive the next wave of innovation in human-machine integration.

In the coming years, we can expect AI-powered BCIs to become more intuitive, efficient, and accessible, with far-reaching impacts on healthcare, rehabilitation, and everyday life. Dr. Pulicharla's research marks an important step in this journey, paving the way for future breakthroughs in this rapidly evolving field.

For a deeper dive into this pioneering work, read the full article here: AI-powered Neuroprosthetics for Brain-Computer Interfaces (BCIs).



Coarse-graining a cortex at different scales. A: Example original pial surface from a healthy human viewed from varying angles. B: Same example cortical surface from A, coarse-grained to different spatial scales. Top row shows resulting pial surfaces (with a small amount of smoothing applied for visualization purposes here). Bottom row shows the corresponding voxelisation at each scale through the slice indicated by blue plane in panel A. Note that the actual size of the brains for analysis are rescaled; we display all brains scaled at an equal size here for the ease of visualization of the method. Credit: (2024). DOI: 10.7554/eLife.92080.3© Provided by Phys.org

Study identifies universal blueprint for mammalian brain shape

Researchers have developed a new approach for describing the shape of the cerebral cortex, and provide evidence that cortices across mammalian species resemble a universal, fractal pattern.

The study, published as a Reviewed Preprint in *eLife* and appearing today as a revised version, is described by the editors as a valuable framework for our

understanding of the brain cortex as a fractal shape. They describe the strength of evidence as convincing for a universal blueprint for mammalian cerebral cortex folding.

With further research and validation, the approach could be used to grant insights into the development of various degenerative and congenital neuropathic conditions.

The cerebral cortex is the outermost layer of the brain, and is responsible for complex functions such as thought, perception and decision-making. Cerebral cortex folding, known as gyrification, is the process by which the brain's surface develops grooves (sulci) and ridges (gyri). This folding increases the surface area of the brain, allowing for a greater number of neurons and more complex information processing. The cortex displays a wide diversity of shapes and sizes across and within species.

"We set out to find a way to define the shape of the cortex, and express what is unique about the complex shapes and folds that comprise each cortex," says lead author Yujiang Wang, a Future Leaders Fellow at the Computational Neurology, Neuroscience & Psychiatry (CNNP) Lab in the School of Computing, Newcastle University, UK.

"One can look at an image of a cerebral cortex, and recognize what it is. But how can we tell apart your cortex from mine? Or how can we distinguish a giraffe's cerebral cortex from that of a marmoset? This requires a more expressive way to describe the shape of the cortex."

Wang and colleagues began by establishing two key principles. Firstly, they knew that cortices cannot simply assume any folded shape—cortices are thin sheets of gray matter folded in complex ways around white matter, and the degree of folding they undergo is precisely determined by the thickness and size of this sheet. This principle is called universal scaling.

They then devised a way to "melt" the cerebral cortex, by removing folds that were smaller than a certain threshold, allowing them to study the remaining folds individually. This revealed the second principle; that cortices are composed of folds of various sizes, where the small folds resemble their larger folds—a property called self-similarity. This resembles fractal scaling, where a complex

geometric shape exhibits intricate patterns that repeat at progressively smaller scales.

The team then combined these principles of universal scaling and self-similarity to study the cerebral cortex of 11 different primate species, including humans, chimpanzees and marmosets. This revealed that despite the clear visual differences between the species' cortices, all of them follow a universal scaling law, and resemble the same fractal shape. So, if you take the most complex cortex studied, that of a human, and use the team's process of melting to eliminate the smallest folds, it begins to resemble that of a chimpanzee. If you melt the cortex of a chimpanzee, it resembles that of a rhesus monkey, and so on.

These findings suggest that regardless of species, there is only one way for a cerebral cortex to undergo folding. So why are they so clearly different when observed through an MRI scan? They appear different in size, and some are highly folded, like the human cortex, and some are much smoother, like the marmoset cortex.

"The key here is to precisely define what we mean by 'resemble,'" explains senior author Bruno Mota, a Professor at the metaBIO Lab, Instituto de Física, Universidade Federal do Rio de Janeiro, Brazil. "One can imagine a shape that looks like a human cortex, but, as you zoom in, you find within each fold there are infinitely smaller folds. Such a shape cannot exist in nature, but it can be defined mathematically as a fractal shape, as we have done here. What we have shown is that all cortices of the species we have studied resemble this fractal shape for a certain range of fold sizes."

Therefore, Mota adds, the differences observed in cortical shapes across these species are largely due to the fact that each has a different range of fold sizes for which the resemblance holds. For a smoother cortex, like in a marmoset, this range is narrower; for a more folded one, like a chimpanzee, it is broader.

The authors note that their study was limited to descriptions of entire cortical hemispheres, and that in future work they will look to explore more specific cortical regions. They will also investigate how neurodegenerative diseases such as Alzheimer's affect the fractal shape of the cortex. This may eventually allow the identification of more detailed biomarkers for various neurological conditions and diseases, and support further understanding of how they develop.

"Our results suggest a universal blueprint for mammalian brain shape, and a common set of mechanisms governing cortical folding," concludes Mota. "We hope that our framework for expressing and analyzing cortical shape can become a powerful tool to characterize and compare cortices of different species and individuals, across development and aging, and across health and disease."

More information: Yujiang Wang et al, Neuro-evolutionary evidence for a universal fractal primate brain shape, *eLife* (2024). DOI: 10.7554/eLife.92080.3

Provided by eLife

Human intelligence: How cognitive circuitry, rather than brain size, drove its evolution

It's one of the great paradoxes of evolution. Humans have demonstrated that having large brains are key to our evolutionary success, and yet such brains are extremely rare in other animals. Most get by on tiny brains, and don't seem to miss the extra brain cells (neurons).

Why? The answer that most biologists have settled on is that large brains are costly in terms of the energy they require to run. And, given the way natural selection works, the benefits simply don't exceed the costs.

But is it just a matter of size? Does the way our brains are laid out also affect their costs? A new study, published in *Science Advances*, has produced some intriguing answers.

All our organs have running costs, but some are cheap and others expensive. Bones, for example, are relatively cheap. Although they make up around 15% of your weight, they only use 5% of your metabolism. Brains are at the other end of the spectrum, and at about 2% of typical human body weight, running them uses around 20% of our metabolism. And this without doing any conscious thinking—it even happens when we're asleep.

For most animals, the benefits of serious thinking are simply not worth it. But for some reason—the greatest puzzle in human evolution, perhaps—humans found ways to overcome the costs of having a larger brain and reap the benefits.

All this is fairly well known, but there is a more tantalizing question. Certainly humans have to bear the greater costs of our brains because they are so large, but are there different costs because of the special nature of our cognition? Does thinking, speaking, being self-conscious or doing sums cost more than typical day-to-day animal activities?

It's not an easy question to answer, but the team behind the new study, led by Valentin Riedl of the Technical University of Munich, Germany, have risen to the challenge.

The authors had a number of known points to start with. The basic design and structure of neurons is much the same across the brain—and across species. The neuronal density is also the same for humans and other primates, so these are unlikely to be the driver of intelligence. If they were, some animals with large brains such as orcas and elephants would likely be smarter than humans.

They also knew that across human evolution, the neocortex—the largest part of the outermost layer of the brain, known as cerebral cortex—has expanded at a greater rate than other parts. This region, which involves the prefrontal cortex, is responsible for tasks involving attention, thought, planning, perception and episodic memory—all needed for higher cognitive function.

These two observations led them to investigate whether there are different costs of signaling across different regions of the brain.

The team scanned the brains of 30 people using a technique that could simultaneously measure glucose metabolism (a measure of energy consumption) and the level of signaling across the cortex. They could then look at the correlation between these two elements and see whether different parts of the brain used different levels of energy—and if so how.

Surprising findings

Neurobiologists will surely ponder and explore the fine details of the results, but from an evolutionary point of view, they are thought-provoking. What they found is that the difference in energy consumption between different areas of the brain is big. Not all bits of the brain are equal, energetically speaking.

Not only that, but the parts of the human brain that have expanded most had higher costs than expected. The neocortex in fact demanded around 67% more energy than sensorimotor networks per gram of tissue.

This means that during the course of human evolution, not only did the metabolic costs of our brains go up as they became larger, but they did so at an accelerating rate as the neocortex expanded faster than the rest of the brain.

Why should that be the case? A neuron is a neuron, after all. The neocortex relates directly to higher cognitive function.

The signals sent across this area are mediated through brain chemicals such as serotonin, dopamine and noradrenaline (neuromodulators), which create circuits in the brain to help maintain a general level of excitement (in a neurological sense of the word meaning being awake, not having fun). These circuits, which regulate some brain areas more than others, control and modify the ability of neurons across the brain to communicate with each other.

In other words, they keep the brain active for memory storage and thinking—a generally higher level of cognitive activity. Not surprisingly, perhaps, the higher level of activity involved in our advanced cognition comes at a higher energetic cost.

Ultimately then, it seems the human brain evolved to such advanced levels of cognition not just because we have large brains, nor even just because certain areas of our brain grew disproportionately big, but because—at a cost—the connectivity improved.

Many animals with large brains, such as elephants and orcas, are highly intelligent. But it seems it is possible to have a large brain without developing the "right" circuitry for human-level cognition.

The results help us understand why larger brains are so rare. A larger brain can enable more complex cognition to evolve. It is not just a matter of scaling up brains and energy at the same rate though, but taking on additional costs.

This doesn't really answer the ultimate question—how did humans manage to break through the brain-energy ceiling? As so often in evolution, the answer must lie in ecology, the ultimate source of energy. To grow and maintain a large

brain—whatever social, cultural, technological or other things it is used for—requires a dependable and high quality diet.

To learn more, we need to explore the last million years, the period when our ancestors' brains really expanded, to investigate this interface between energy expenditure and cognition.

More information: Gabriel Castrillon et al, An energy costly architecture of neuromodulators for human brain evolution and cognition, *Science Advances* (2023). DOI: 10.1126/sciadv.adi7632

Mammalian brain cells mapped comprehensively, inspiring human studies

Mammalian brain cells mapped comprehensively, inspiring human studies© Provided by Interesting Engineering

Scientists at the Broad Institute of MIT and Harvard have produced an extensive atlas of cell types in a mammalian brain using innovative spatial transcriptomics technology.

This atlas, detailed in the journal *Nature*, delineates several thousand cell populations across the entire mouse brain, shedding light on cellular diversity in previously understudied brain regions.

Mapping the unknown: Uncovering cellular diversity

The research team, led by Evan Macosko and Fei Chen, employed spatial transcriptomics to map gene activity and cell locations within the mouse brain.

The study uncovered an estimated 90 percent of all cell populations, emphasizing the richness of cellular diversity in subcortical brain regions like the midbrain, pons, medulla, and hypothalamus.

Macosko highlighted the significance of studying these areas, stating:

"A lot of the real nuts and bolts stuff that a brain is doing is in these basic areas, which have received very little attention compared to the cortex."

A decade of work: From lab development to atlas creation

The team's approach involved measuring the activity of all genes in individual cells throughout the mouse brain, creating a comprehensive map.

The dataset, comprising over four million gene activity profiles, was then analyzed using the Slide-seq method, identifying nearly 5,000 unique cell populations.

Macosko stressed the importance of their work, stating, "Our atlas represents the culmination of a decade of work at the Broad."

Unlocking brain mysteries: Disease associations and signaling molecules

The atlas revealed insights into cellular functions and potential roles of brain structures in diseases.

The team also explored the use of neurotransmitters by different cell types in various brain regions. Additionally, the atlas demonstrated its utility in pinpointing where disease-associated genes are active, offering valuable information on conditions like schizophrenia.

This study is part of a larger initiative, with 10 papers in *Nature* collectively providing the first complete cell type atlas of a whole mammalian brain.

Macosko emphasized the importance of their work in paving the way for future efforts, stating:

"By mapping the mouse brain, the primary mammalian system used in neuroscience, we've provided molecular, functional, and anatomical classifications that provide a key foundation for human brain mapping, which is what comes next."

Deciphering the molecular language of brain cells

In a parallel study, UC San Diego researchers have contributed to understanding brain cell diversity. Analyzing over 2.3 million brain cells from mice, the researchers created a comprehensive mouse brain map and employed artificial intelligence to predict DNA regions determining cell types.

The study, part of the National Institutes of Health's Brain Research Through Advancing Innovative Neurotechnologies Initiative, adds to the growing knowledge of brain cell types, providing a baseline for comparisons of neurological and psychiatric disorders.

The researchers also compared brains across species, discovering that cell-type-specific gene expression patterns evolve rapidly.

This finding enhances our understanding of the brain's evolution and the diversity of cell types. Joseph Ecker of the Salk Institute highlighted the importance of incorporating data from various mammalian species, stating:

"By filling in these gaps with other mammalian species, we can continue to answer those questions and improve the machine-learning models we use by providing them more data."

Unlocking disease secrets: Implications for neuropsychiatric disorders

Insights from this research already offer relevance to human diseases, as genetic programs determining cell types were found in genome regions linked to diseases like multiple sclerosis, anorexia nervosa, and tobacco use disorder.

Senior author Bing Ren emphasized the impact of this research on targeted therapies, stating:

"We hope this will pave the way for more precise, targeted therapies that can heal diseased cells without affecting the rest of the brain."

For example, Louis Pasteur and Robert Koch, among other researchers in this era, succeeded for the first time in attributing a number of infectious diseases to certain microbial organisms in the sense of a "germ theory."

For the longest time in human history, various infectious diseases were among the main causes of death and led to people dying much earlier on average than today, often in childhood. It was not until the end of the 19th century that newly acquired scientific knowledge led to extensive hygiene measures being introduced in the interests of public health.

At around the same time, the first vaccines were also applied to prophylactically suppress certain viral pathogens and the diseases they cause at a population level. Thanks to the systematic introduction of antibiotic agents on a large scale from the second half of the 20th century onward, it also became possible to greatly reduce bacterial infections.

Perfect balance: How the brain fine-tunes its sensitivity

A sensitive perception of the environment is crucial for guiding our behavior. However, an overly sensitive response of the brain's neural circuits to stimuli can lead to neurodevelopmental disorders such as epilepsy. University of Basel researchers report in the journal *Nature* how neuronal networks in the mouse brain are fine-tuned.

We are constantly exposed to a wide range of sensory stimuli, from loud noises to whispers. In order to efficiently process these diverse stimulus intensities, the brain needs to strike a balance in its responsiveness. An excessive sensitivity triggers an over-activation of nerve cells in response to a stimulus, leading to epileptic seizures. Conversely, insufficient sensitivity results in a reduced ability to perceive and discriminate stimuli.

But how does the brain manage to be highly sensitive without becoming over-activated? "The key lies in maintaining a balance between neural excitation and inhibition," explains Professor Peter Scheiffele from the Biozentrum, University of Basel.

"In mouse models, we have now discovered how this balance is maintained to ensure stable brain function." The study particularly focused on the neocortex, a brain area responsible for perception and a range of complex functions such learning.

Our brain consists of billions of interconnected nerve cells that interact through so-called synapses and process sensory stimuli such as sounds, touch, and sights. While excitatory neurons pass on the input signal, inhibitory neurons control the timing and intensity of the information flow. This internal control system ensures that the nervous system responds appropriately to stimuli.

Neurons are able to detect an elevated neuronal network activity and subsequently reduce the system's sensitivity to stimuli. But how the cells are instructed at the molecular level was poorly understood.

"We have now revealed that highly activated excitatory neurons release a protein called BMP2," says lead author Dr. Zeynep Okur. "BMP2 signals to the inhibitory neurons, initiating a genetic program that leads to the formation of new synapses." These additional synapses increase the impact of inhibitory neurons and dampen network activity.

This feedback mechanism is critical for tuning the sensitivity of neuronal networks, preventing over-activation and thus excessive responses to stimuli. "Switching-off the BMP2-induced genetic program in inhibitory neurons triggers epileptic seizures in mice, but only when they are older," explains Okur. Thus, this process is involved in long-term adaptations of cortical networks.

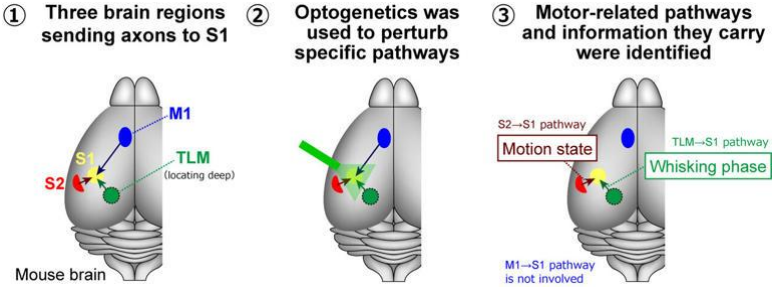
The BMP2 signaling pathway has been known for its role in early brain developmental, particularly in nerve cell differentiation. "We have been able to show that this pathway is re-purposed to stabilize neuronal circuits in the adult brain," emphasizes Scheiffele. This plays an important role for brain plasticity in adulthood—the basis for learning and memory.

"We now understand at the molecular level how neural networks balance excitation and inhibition," says Scheiffele. "With our work, we are expanding the repertoire of options to treat epilepsy and other neurodevelopmental disorders." Targeted interventions in the BMP2 signaling pathway could help to fine-tune and re-adjust brain sensitivity.

More information: Zeynep Okur et al, Control of neuronal excitation–inhibition balance by BMP–SMAD1 signalling, *Nature* (2024). DOI: 10.1038/s41586-024-07317-z

Provided by University of Basel

Study challenges traditional views on how the brain processes movement and sensation



Utilizing optogenetics, researchers at Fujita Health University have selectively deactivated neural pathways with light, revealing new insights into how sensory and motor areas of the mouse brain communicate during movement. Credit: Takayuki Yamashita from Fujita Health University© Provided by Medical Xpress

Our body movements profoundly impact how our brain processes sensory information. Historically, it was believed that the brain's primary motor cortex played a key role in modulating sensory experiences during movement. However, a new study led by researchers from Fujita Health University has challenged this view.

By selectively inhibiting different neural pathways in the mouse brain, they discovered that regions beyond the primary motor cortex significantly influence the primary sensory cortex during movement.

The brain is widely considered the most complex organ in the human body. The intricate mechanisms through which it processes sensory information and how this information affects and is affected by motor control have captivated neuroscientists for more than a century. Today, thanks to advanced laboratory

tools and techniques, researchers can use animal models to solve this puzzle, especially in the mouse brain.

During the 20th century, experiments with anesthetized mice proved that sensory inputs primarily define neuronal activity in the primary sensory cortices—the brain regions processing sensory information, including touch, vision, and audition.

However, over the past few decades, studies involving awake mice revealed that spontaneous behavior, such as exploratory motion and movement of the whiskers called whisking, actually regulates the activity of the sensory responses in the primary sensory cortices. In other words, sensations at the neuronal level appear substantially modulated by body movements, even though the corresponding neuronal circuits and the underlying mechanisms are not fully understood.

To address this knowledge gap, a research team from Japan investigated the primary somatosensory barrel cortex (S1)—a region of the mouse brain that handles tactile input from the whiskers. Their latest study, published in *The Journal of Neuroscience* was conducted by Professor Takayuki Yamashita from Fujita Health University (FHU) and Dr. Masahiro Kawatani, affiliated with FHU and Nagoya University, along with their team.

The S1 region receives input through the axons from several other areas, including the secondary somatosensory cortex (S2), the primary motor cortex (M1), and the sensory thalamus (TLM).

To investigate how these regions modulate activity in S1, the researchers turned to optogenetics (a technique for controlling activities of specific neuronal populations by light) involving eOPN3, which is a recently discovered light-sensitive protein enabling effective inhibition of specific neural pathways in response to light. Using viruses as a vector, they introduced the gene coding for this protein into the M1, S2, and TLM regions in mice.

Then, they measured neural activity in S1 in awake mice performing spontaneous whisking. During this process, they selectively inhibited different signal inputs going to S1 using light as an ON/OFF switch and observed the effect at S1.

Interestingly, only signal inputs from S2 and TLM to S1, not from M1 to S1, modulated neuronal activity in S1 during spontaneous whisking. Specifically, the pathway from S2 to S1 seems to convey information about the motion state of the whiskers.

Additionally, the TLM-to-S1 pathway appeared to relay information related to the phase of spontaneous whisking, which follows a repetitive and rhythmic pattern.

These results challenge the established view that neuronal activity in sensory cortices is modulated primarily by motor cortices during movement; as Prof. Yamashita remarks, "Our findings provoke a reconsideration of the role of motor-sensory projections in sensorimotor integration and bring to light a new function for S2-to-S1 projections."

A better understanding of how distinct brain regions modulate activities among each other in response to movement could lead to progress in myriad applied fields. These research insights have far-reaching implications, potentially revolutionizing fields like artificial intelligence (AI), prosthetics, and brain-computer interfaces.

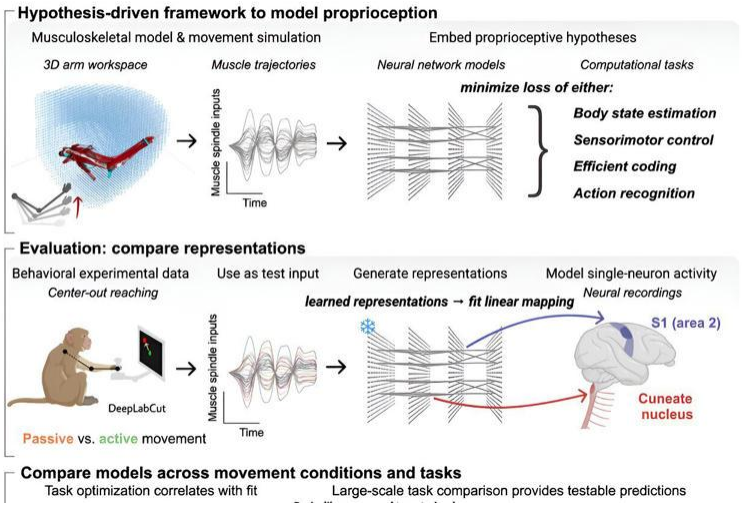
"Understanding these neural mechanisms could greatly enhance the development of AI systems that mimic human sensory-motor integration and aid in creating more intuitive prosthetics and interfaces for those with disabilities," Prof. Yamashita adds.

In summary, this study sheds light on the intricate workings of the brain. It also paves the way for researching the connection between body motion and sensory perception. As we continue to explore brain-related enigmas, studies like this offer vital clues in our quest to understand the most complex organ in the human body.

More information: Masahiro Kawatani et al, Interareal synaptic inputs underlying whisking-related activity in the primary somatosensory barrel cortex, *The Journal of Neuroscience* (2023). DOI: 10.1523/JNEUROSCI.1148-23.2023

Provided by Fujita Health University

Unraveling the 'sixth sense': New study explores how the brain senses body position and movement



Graphical abstract. Credit: Cell (2024). DOI: 10.1016/j.cell.2024.02.036© Provided by Medical Xpress

How does your brain know the position and movement of your different body parts? The sense is known as proprioception, and it is something like a "sixth sense," allowing us to move freely without constantly watching our limbs.

Proprioception involves a complex network of sensors embedded in our muscles that relay information about limb position and movement back to our brain. However, little is known about how the brain puts together the different signals it receives from muscles.

A new study led by Alexander Mathis at EPFL now sheds light on the question by exploring how our brains create a cohesive sense of body position and movement. Published in *Cell*, the study was carried out by Ph.D. students Alessandro Marin Vargas, Axel Bisi, and Alberto Chiappa, with experimental data from Chris Versteeg and Lee Miller at Northwestern University.

"It is widely believed that sensory systems should exploit the statistics of the world, and this theory could explain many properties of the visual and auditory system," says Mathis. "To generalize this theory to proprioception, we used musculoskeletal simulators to compute the statistics of the distributed sensors."

The researchers used this musculoskeletal modeling to generate muscle spindle signals in the upper limb to generate a collection of "large-scale, naturalistic movement repertoire." They then used this repertoire to train thousands of "task-driven" neural network models on sixteen computational tasks, each of which reflects a scientific hypothesis about the computations carried out by the proprioceptive pathway, which includes parts of the brainstem and somatosensory cortex.

Our brains take rhythmic snapshots of the world as we walk

For decades, psychology departments around the world have studied human behavior in darkened laboratories that restrict natural movement.

Our new study, published today in *Nature Communications*, challenges the wisdom of this approach. With the help of virtual reality (VR), we have revealed previously hidden aspects of perception that happen during a simple everyday action—walking.

We found the rhythmic movement of walking changes how sensitive we are to the surrounding environment. With every step we take, our perception cycles through "good" and "bad" phases.

This means your smooth, continuous experience of an afternoon stroll is deceptive. Instead, it's as if your brain takes rhythmic snapshots of the world—and they are synchronized with the rhythm of your footfall.

The next step in studies of human perception

In psychology, the study of visual perception refers to how our brains use information from our eyes to create our experience of the world.

Typical psychology experiments that investigate visual perception involve darkened laboratory rooms where participants are asked to sit motionless in front of a computer screen.

Often, their heads will be fixed in position with a chin rest, and they will be asked to respond to any changes they might see on the screen.

This approach has been invaluable in building our knowledge of human perception, and the foundations of how our brains make sense of the world. But these scenarios are a far cry from how we experience the world every day.

This means we might not be able to generalize the results we discover in these highly restricted settings to the real world. It would be a bit like trying to understand fish behavior, but only by studying fish in an aquarium.

Instead, we went out on a limb. Motivated by the fact our brains have evolved to support action, we set out to test vision during walking—one of our most frequent and everyday behaviors.

A walk in a (virtual) forest

Our key innovation was to use a wireless VR environment to test vision continuously while walking.

Several previous studies have examined the effects of light exercise on perception, but used treadmills or exercise bikes. While these methods are better than sitting still, they don't match the ways we naturally move through the world.

Instead, we simulated an open forest. Our participants were free to roam, yet unknown to them, we were carefully tracking their head movement with every step they took.

We tracked head movement because as you walk, your head bobs up and down. Your head is lowest when both feet are on the ground and highest when swinging your leg in-between steps. We used these changes in head height to mark the phases of each participant's "step-cycle."

Participants also completed our visual task while they walked, which required looking for brief visual "flashes" they needed to detect as quickly as possible.

By aligning performance on our visual task to the phases of the step-cycle, we found visual perception was not consistent.

Instead, it oscillated like the ripples of a pond, cycling through good and bad periods with every step. We found that depending on the phases of their step-cycle, participants were more likely to sense changes in their environment, had faster reaction times, and were more likely to make decisions.

Oscillations in nature, oscillations in vision

Oscillations in vision have been shown before, but this is the first time they have been linked to walking.

Our key new finding is these oscillations slowed or increased to match the rhythm of a person's step-cycle. On average, perception was best when swinging between steps, but the timing of these rhythms varied between participants. This new link between the body and mind offers clues as to how our brains coordinate perception and action during everyday behavior.

Next, we want to investigate how these rhythms impact different populations. For example, certain psychiatric disorders can lead to people having abnormalities in their gait.

There are further questions we want to answer: are slips and falls more common for those with stronger oscillations in vision? Do similar oscillations occur for our perception of sound? What is the optimal timing for presenting information and responding to it when a person is moving?

Our findings also hint at broader questions about the nature of perception itself. How does the brain stitch together these rhythms in perception to give us our seamless experience of an evening stroll?

These questions were once the domain of philosophers, but we may be able to answer them, as we combine technology with action to better understand natural behavior.

Study finds 'brain endurance training' boosts cognitive and physical abilities in older adults

The research has implications for healthy aging. Previous studies have shown that mental fatigue can impair both cognitive and physical performance, including poorer balance control, leading to increased risk of falls and accidents. This study, published in *Psychology of Sport and Exercise*, is the first to examine the benefits of BET for both cognitive and physical performance in older adults.

Corresponding author Professor Chris Ring said, "We have shown that BET could be an effective intervention to improve cognitive and physical performance in older adults, even when fatigued. This could have significant implications for improving health span in this population, including reducing the risk of falls and accidents."

In the experiment, 24 healthy sedentary women aged between 65-78 were allocated to one of three training groups: brain endurance training (BET), exercise training, and no training (control group). The first two groups each completed three 45-minute exercise sessions per week over a period of eight weeks. Each session included 20 minutes of resistance training and 25 minutes of endurance training. While the exercise sessions were the same for each of these groups, the BET group also completed a 20-minute cognitive task prior to exercising.

All three groups completed a series of cognitive (reaction time and color-matching tests) and physical tests (walk, chair-stand and arm-curl tests) to assess performance at the start and end of the study. Participants in the BET group outperformed the exercise-only group in the cognitive tasks, with a 7.8% increase in cognitive performance after exercise, compared to a 4.5% increase in the exercise-only group. In terms of physical performance, the BET group achieved a 29.9% improvement, compared to 22.4% for the exercise-only group.

"BET is an effective countermeasure against mental fatigue and its detrimental effects on performance in older adults," added Professor Ring. "While we still need to extend our research to include larger sample sizes including both men

and women, these promising initial findings show we should do more to encourage older people to engage in BET to improve brain and body activities."

More information: Jesús Díaz-García et al, Brain endurance training improves sedentary older adults' cognitive and physical performance when fresh and fatigued, *Psychology of Sport and Exercise* (2024). DOI: 10.1016/j.psychsport.2024.102757

Provided by University of Birmingham

Machine Learning Helps Scientists Locate the Neurological Origin of Psychosis

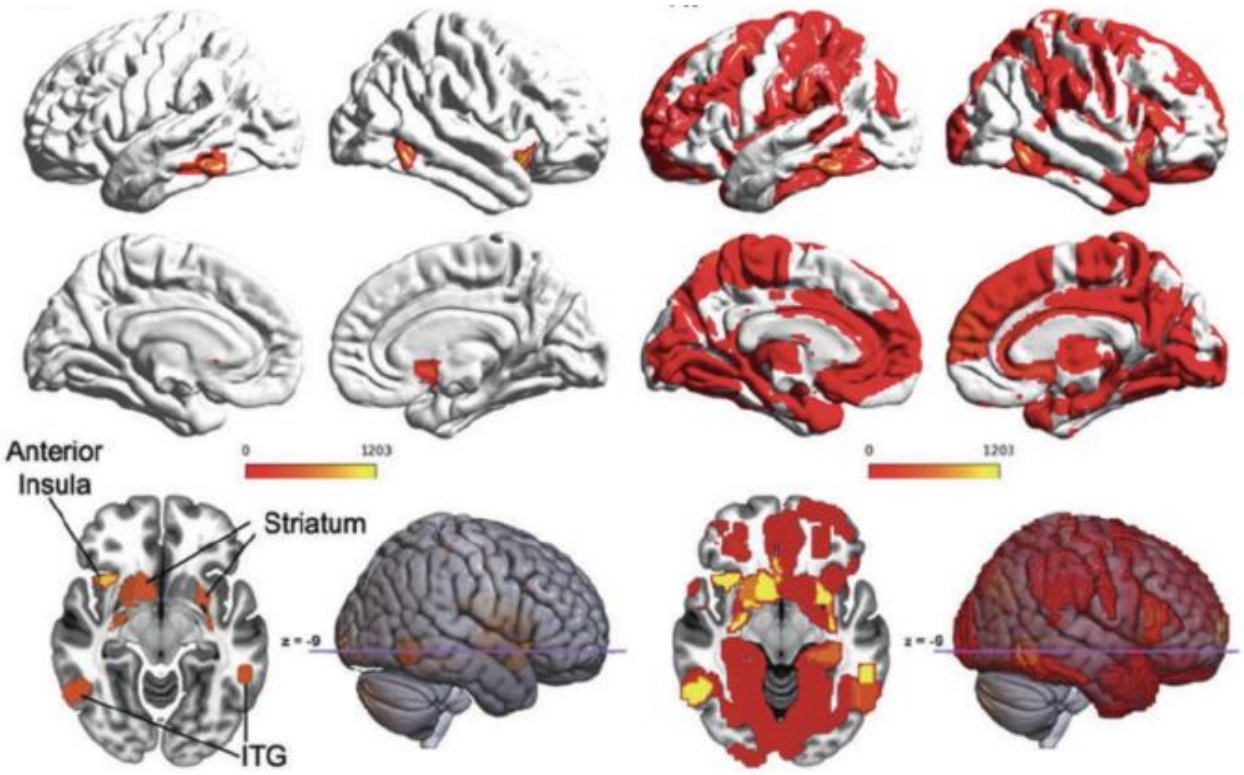
Researchers in the United States, Chile, and the United Kingdom have leveraged machine learning to hone in on the parts of the brain responsible for psychosis. Their findings help to illuminate a common yet elusive experience and could contribute to the development of novel treatments for psychosis and the conditions that cause it.

Around 3 in every 100 people will experience at least one psychotic episode in their lifetimes. Commonly misunderstood, these episodes are characterized by hallucinations (a false perception involving the senses) or delusions (false beliefs not rooted in reality). Many people who experience psychosis have a condition like schizophrenia or bipolar disorder; others have a history of substance abuse, and still others have no particular condition at all.

Regardless of its cause, psychosis can be debilitating for those who experience it, leading some people to seek out antipsychotic medication aimed at staving off future episodes. Though antipsychotic medications are often a godsend for the people who take them, they've historically disrupted neurological psychosis research. During brain scans, it's difficult to know whether specific brain activity can be attributed to the person's condition or to the drugs they're taking. This means medical professionals and pharmaceutical companies work with a fairly limited understanding of psychosis as they help patients manage their episodes.

Researchers at Stanford University, the University of California Los Angeles, Universidad del Desarrollo, and the University of Oxford relied on two strategies to circumvent this issue. To start, they gathered study participants from a wide

range of ages and conditions in the hope of uncovering an overarching theme. The group of nearly 900 participants included people ages 6 to 39, some of whom had a history of psychosis or schizophrenia and some of whom had never experienced either. Just over 100 participants had 22q11.2 deletion syndrome, meaning they're missing part of one of their copies of chromosome 22—a condition known to carry a 30% risk of experiencing psychosis, schizophrenia, or both. Another 120 participants experienced psychosis but had not been diagnosed with any particular hallucination- or delusion-causing condition.



3D visualizations of the brains of those who experience psychosis and those who don't.© Provided by ExtremeTech

Credit: Supekar et al, Molecular Psychiatry/DOI 10.1038/s41380-024-02495-8

The team also used machine learning to spot the minute distinctions between the brain activity of those who experience psychosis and the brain activity of those who don't. To map out the participants' neurological activity, the team used functional magnetic resonance imaging (fMRI). This technique allows medical professionals and researchers to track the tiny fluctuations in blood flow triggered by brain changes.

With a custom spatiotemporal deep neural network (stDNN), the researchers compared the functional brain signatures of all participants and found among

those with 22q11.2 deletion syndrome. Regardless of demographic, these participants experienced what appeared to be "malfunctions" in the anterior insula and the ventral striatum. These two parts of the brain are involved in humans' cognitive filters and reward predictors, respectively. The stDNN continued to find clear discrepancies between the anterior insulae and ventral striata of those who experienced psychosis and those who did not, further indicating that these two regions of the brain played a vital role in hallucinations and delusions.

These findings, shared Friday in a paper for *Molecular Psychiatry*, support a standing theory regarding the reliance of psychosis on malfunctioning cognitive filters. Scientists have long wondered whether, during a psychotic episode, the brain struggles to distinguish what's true from what isn't. This is a key function of the brain's salience network, which detects and assigns importance to incoming stimuli. When the salience network cannot work correctly, the brain might incorrectly assign importance and attention to the wrong stimuli, resulting in a hallucination or delusion.

“Our discoveries underscore the importance of approaching people with psychosis with compassion,” said Stanford neuroscientist and senior study author Dr. Vinod Menon in a statement. Menon and his colleague, psychiatrist Kaustubh Supekar, hope their findings will assist in the development of antipsychotic treatments, especially for those with schizophrenia.

Composition of gut microbiota could influence decision-making

The way we make decisions in a social context can be explained by psychological, social, and political factors. But what if other forces were at work? Hilke Plassmann and her colleagues from the Paris Brain Institute and the University of Bonn show that changes in gut microbiota can influence our sensitivity to fairness and how we treat others. Their findings are published in the journal *PNAS Nexus*.

The intestinal microbiota—i.e., all the bacteria, viruses and fungi that inhabit our digestive tract—plays a pivotal role in our bodies, well beyond digestive function. Recent research underscores its impact on cognition, stress, anxiety, depressive

symptoms, and behavior; mice raised in a sterile environment, for example, have difficulty interacting with other individuals.

While these findings are promising, most of this research is carried out on animals and cannot be extrapolated to humans. Nor does it allow us to understand what neuronal, immune, or hormonal mechanisms are at work in this fascinating dialogue between brain and intestine: researchers observe a link between the composition of the microbiota and social skills but do not know precisely how one controls the other.

"The available data suggests that the intestinal ecosystem communicates with the central nervous system via various pathways, including the vagus nerve," explains Plassmann (Sorbonne University), head of the Control-Interoception-Attention Team at the Paris Brain Institute, and professor at Insead. "It might also use biochemical signals that trigger the release of neurotransmitters, such as dopamine and serotonin, which are essential for proper brain function."

Studying altruistic punishment

To determine whether the composition of the human gut microbiota could influence decision-making in a social setting, the researcher and her colleagues used behavioral tests—including the famous "ultimatum game" in which one player is given a sum of money he must split (fairly or unfairly) with a second player, who is free to decline the offer if she deems it insufficient. In that case, neither player receives any money.

Refusing the sum of money is equivalent to what we call "altruistic punishment," i.e., the impulse to punish others when a situation is perceived as unfair: for the second player, restoring equality (no one receives any money) sometimes feels more important than obtaining a reward. The ultimatum game is then used as an experimental way of measuring sensitivity to fairness.

To fully exploit this effect, the researchers recruited 101 participants. For seven weeks, 51 took dietary supplements containing probiotics (beneficial bacteria) and prebiotics (nutrients that promote the colonization of bacteria in the gut),

while 50 others received a placebo. They all participated in an ultimatum game during two sessions at the beginning and end of the supplementation period.

Are bacteria pulling the strings?

The study's results indicate that the group that received the supplements was much more inclined to reject unequal offers at the end of the seven weeks, even when the money split was slightly unbalanced. Conversely, the placebo group behaved similarly during the first and second test sessions.

Moreover, the behavioral change in the supplemented group was accompanied by biological changes: the participants who, at the start of the study, had the greatest imbalance between the two types of bacteria that dominate the gut flora (Firmicutes and Bacteroidetes) experienced the most significant change in the composition of their gut microbiota with the intake of supplements. In addition, they also showed the greatest sensitivity to fairness during the tests.

The researchers also observed a sharp drop in their levels of tyrosine, a dopamine precursor, after the seven-week intervention. For the first time, a causal mechanism is emerging: the composition of the gut microbiota could influence social behavior through the precursors of dopamine, a neurotransmitter involved in brain reward mechanisms.

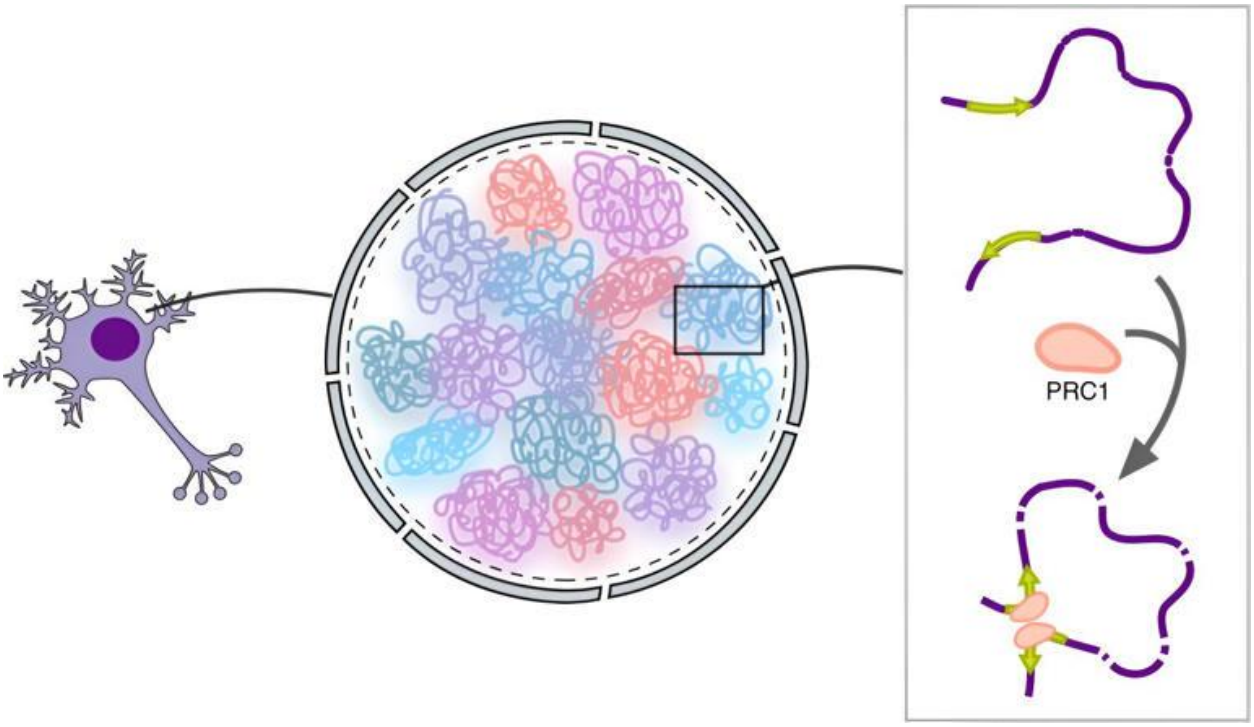
"It's too early to say that gut bacteria can make us less rational and more receptive to social considerations," concludes Plassmann. "However, these new results clarify which biological pathways we must look at. The prospect of modulating the gut microbiota through diet to positively influence decision-making is fascinating. We need to explore this avenue very carefully."

More information: Marie Falkenstein et al, Impact of the gut microbiome composition on social decision-making, *PNAS Nexus* (2024). DOI: 10.1093/pnasnexus/pgae166

Provided by Paris Brain Institute

Study reveals differences in DNA folding between neurons and other brain cells, links them to cell functions

Left to right: a neuron, its nucleus, and repressive DNA contacts. Credit: Ilya Pletenev© Provided by Phys.org



Researchers from Skoltech and their colleagues have investigated nerve cell regulation. Mounting knowledge of regulation mechanisms could enable a better understanding of how the healthy brain operates and what goes wrong in developmental and oncological diseases associated with regulation errors. The study is published in the journal *Nucleic Acids Research*.

With a few exceptions, all the cells in an organism contain the same DNA. Despite this, even within one organ, there are cells of distinct types that vary widely in how they look and behave. The nervous tissue in the brain, for example, is composed of neurons, which transmit the signals, and the supporting glial cells.

Such specialization is the result of gene regulation, i.e., the selective activation and deactivation of the genes encoded in the DNA. It can occur both during a cell's initial development and in a mature cell.

One of the main mechanisms of gene regulation relies on three-dimensional structure. The way the several meters of DNA per cell nucleus are folded in 3D space makes it possible to switch certain genes on or off at a particular stage in the cell's life or for specific cell types.

Even among neurons, there are those of the excitatory and the somewhat rarer inhibitory variety, and these two breeds of nerve cells must run distinct genetic programs: They require different genes to be active. Appropriate DNA folding is a key mechanism that enables this.

"In this particular study, we demonstrated that the genes a neuron needs to be off tend to be close to one another in space, even though they might have been far away if you were to straighten out the DNA into a long one-dimensional strand. We think this probably makes it easier for repressor proteins to turn off those genes en masse.

"Also, we showed that the DNA of neurons and glial cells forms loops in different places. Moreover, it is the genes important for the cell type in question that tend to bunch up at the base of a loop, possibly making it easier for activator proteins to simultaneously switch them on."

More information: Ilya A Pletenev et al, Extensive long-range polycomb interactions and weak compartmentalization are hallmarks of human neuronal 3D genome, *Nucleic Acids Research* (2024). DOI: 10.1093/nar/gkae271

Provided by Skolkovo Institute of Science and Technology

Neuroscientists discover small group of dopamine neurons play critical role in controlling range of behaviors

A finding by a McGill-led team of neuroscientists could open doors to new treatments for a range of psychiatric and neurological disorders attributed to dysfunctions in specific dopamine pathways.

For those struggling with a psychiatric disorder such as schizophrenia, addiction or ADHD, or with neurological disorders such as Parkinson's disease or Alzheimer's, there might be good news ahead. The neuroscientists have

discovered that a small group of dopamine neurons in the striatum play a crucial role in balancing several essential brain functions, including those related to reward, cognition and movement.

Dopamine is a messenger molecule that is often associated with pleasure and reward. But it plays an equally important role in mood regulation, sleep and digestion, as well as in motor and cognitive functions. An excess release of dopamine, induced by certain drugs or behaviors, is responsible for addiction. Conversely, its absence can cause profound alterations in motor control, as is the case in Parkinson's disease.

A critical balancing act

Scientists had previously identified the functions of two distinct pathways and types of dopamine receptors in the forebrain: the D1 receptors, which activate neurons, and the D2 receptors, which inhibit them. A third group of dopamine receptors that possess both D1 and D2 dopamine receptors was known to exist, but until now, no one had been able to identify their specific function.

By using innovative genetic tools to specifically target these dopamine receptors, which comprise just five percent of the dopamine neurons in the striatum, the researchers were able to begin to understand their functions.

The researchers discovered that this group of neurons present unique cellular characteristics in response to dopamine and are at the origin of a new pathway that is essential for the balance of forebrain functioning. It ensures motor control under normal physiological conditions and curbs hyperactivity induced by psychostimulant drugs.

"Without these neurons, the entire brain systems under dopamine control would become overactive and uncontrollable, since they act to balance the functions of the two types of dopamine receptors in the brain which either facilitate or inhibit the activation of the two pathways we already knew of," explains Bruno Giros, a professor in McGill's department of psychiatry and a researcher at the Douglas Hospital Research Institute. He is the senior author of a recent article on the subject published in *Nature Neuroscience*.

"It's a very exciting finding for us because we've been working on this specific project for close to eight years in collaboration with a team at Université Libre de Bruxelles (ULB)."

For Giros, the discovery comes after 30 years of work in the field, including alongside renowned neuroscientist Marc Caron and 2012 Nobel prize winner Robert J. Lefkowitz as a postdoctoral fellow at Duke University Medical Centre.

"We are only in the early days of working with the tools that we developed to help us to identify this pathway," adds Alban de Kerchove d'Exaerde from the Neurophy Lab at ULB, who collaborated on the research. "I'm sure that a lot of laboratories will work with our tools and will, with time, discover more about the important role that this very specific pathway plays in various fields."

Giros adds, "Now that we understand how this third pathway controls motor functions, the next goal of our research will be to understand more precisely how it is implicated in the control of cognitive processes, and how it could be impaired in psychiatric disorders."

More information: Patricia Bonnavion et al, Striatal projection neurons coexpressing dopamine D1 and D2 receptors modulate the motor function of D1- and D2-SPNs, *Nature Neuroscience* (2024). DOI: 10.1038/s41593-024-01694-4

Provided by McGill University

People with depression could administer brain stimulation at home, trial shows

People with major depression could alleviate their symptoms by self-administering a form of electrical brain stimulation at home, according to a clinical trial of the therapy.

Patients who took a 10-week course of the treatment were about twice as likely to see their depression go into remission than those in a control group who performed the same procedure with the current switched off.

The findings suggest that people with depression could receive beneficial brain stimulation without having to attend a clinic and that the treatment could become an effective alternative for those who do not want, or do not respond to, more traditional therapies.

“This is a potential first line treatment for depression,” said Cynthia Fu, a professor of affective neuroscience and psychotherapy at King’s College London and senior author on the study.

“It can also be used for people whose depression hasn’t improved with antidepressant medication, for people who don’t like antidepressant medication, or who don’t want psychotherapy.”

For the phase two trial, 174 people with major depressive disorder were given a headset to deliver what is known as transcranial direct current stimulation (tDCS). The headset, produced by Flow Neuroscience, which also funded the trial, contains two electrodes that apply a weak current of up to 2 milliamps to the forehead.

The 10-week course was supervised in real-time over video conference calls, starting with five 30-minute sessions a week for three weeks, followed by three 30-minute sessions a week for the next seven weeks.

While half the participants received electrical brain stimulation as expected, the other half unknowingly had “inactive” therapy, where the device delivered a brief, weak current at the start and finish of the session, but was otherwise not providing any stimulation.

Writing in the journal Nature Medicine, the researchers report that depression improved in both groups over the 10-week course, according to their scores on standard depression scales.

But those who had active brain stimulation improved most. The remission rate in the brain stimulation group was 44.9% compared with 21.8% in the inactive control group.

An estimated 5% of adults globally live with depression. The most common treatments are antidepressants and psychological therapies but more than a third of people with major depressive disorder do not reach full clinical remission.

tDCS makes neurons in frontal regions of the brain fire more readily, an effect that is thought to have a beneficial impact on the broader brain network affected by depression.

“We did see a placebo effect, with people who were receiving the inactive treatment showing an improvement,” Fu told the Guardian. “But there were more people in the active treatment arm whose depression improved than in the inactive treatment arm.”

tDCS is already used to treat conditions such as psychosis and eating disorders, and trials so far suggest the procedure is safe. The current delivered to the brain is at least 400 times weaker than that used in electroconvulsive therapy, which induces a generalised seizure in the brain. To reduce any risks from prolonged stimulation, the device shuts off after 30 minutes.

“Although tDCS for depression has been in Nice [National Institute for Health and Care Excellence] guidelines since 2015 and is considered ‘safe’, uncertainties about its efficacy remain,” said Myles Jones, a senior lecturer in psychology at the University of Sheffield, who was not involved in the study.

“This study demonstrates that repeated home use of tDCS is associated with a reduction in a key depression measure.”

He added: “Although single doses of tDCS have proved equivocal in changing neural activity and cognitive performance, prolonged use over days or weeks has been shown to be clinically effective in depression, tinnitus and a range of conditions.”

The Gold Standard For Measuring Brain Activity Has Been Around For 100 Years

Jena, Germany, 1924: Working in near-isolation and with painstaking tediousness, the psychiatrist Hans Berger observes rhythmic electrical activity from the scalp of

human subjects. He is convinced the activity arises from within the brain and coins the term "electroencephalogram."

It is 10 years before the scientific community accepts Berger's work, birthing the field of electroencephalography, or EEG for short.

Today, the electroencephalogram – also abbreviated as EEG – is widely known as a medical test measuring brain electrical activity that's used on patients who have or are suspected to have neurological disorders. The EEG provides a window into the living brain, with a continuous electrical readout of what is happening inside our heads. The procedure may be short, often just a 30-minute recording. But for patients monitored for diagnosis or treatment of brain disease, it can be continued for much longer – days or even weeks.

As a neurologist specializing in epilepsy, I use EEG on a daily basis. Our team at the University of Florida interprets thousands of EEGs a year in neurological patients. I also run a research lab where our goal is to understand the basic structure of the EEG in health and disease.

A history of unexpected twists

The story of EEG is colorful and littered with fables. Berger's interest in brain electricity was not to combat disease, though that was his day job as a physician, but to find a biological basis for his belief in telepathy. He wondered whether the brain waves of EEG could convey thoughts through space, allowing people to read each other's minds. He was unsuccessful in his mission, but the field he founded nonetheless took off.

By the mid-1930s, researchers had observed the striking differences between the awake and asleep EEG. The EEGs of patients with brain disease turned up a variety of unprecedented observations.

And then came a defining moment for modern medicine. In December 1934, a group of Boston physicians observed the rhythmic EEG spike-wave appearance of seizures in patients with "petit mal" epilepsy. Petit mal is an anachronistic term for a type of epilepsy where a patient's flow of thought, speech, or action momentarily freezes during seizures. For the first time, the symptoms and

behavior of patients during seizures were correlated to a brain signal occurring in lockstep.

EEG quickly evolved from a scientific curiosity to a mainstream clinical tool. The first clinical EEG laboratory was set up at Massachusetts General Hospital in 1937. The practice grew in the ensuing decades into the specialized services that institutions like ours have offered since the 1970s.

The EEG explained

So what, exactly, is the EEG?

Imagine taking two small metallic discs connected by a conducting wire. Place one disc on the scalp and connect the other to a neutral reference, such as the ear. Watch a tiny alternating current flow in the wire, proportional to the electrical activity sensed by the conducting contact. This activity is the EEG, the electrical milieu that bathes brain tissue.

In turn, the EEG arises from the excitable nature of nerve cells or neurons. When neurons fire, action potentials – brief, high-voltage spikes traveling outward from their cell bodies – set up local electrical activity in other neurons, causing current to flow within and outside them.

These local current flows may cause the targeted neurons to fire in turn and set up yet more current flows. Thus, the system sustains itself. The average overall activity is a mix of many different frequencies, with the five main ones called delta, theta, alpha, beta, and gamma waves.

If the EEG were just random up-and-down drift – "the bloodless dance of action potentials," commented a skeptical early 20th century neurologist – it would be much less interesting. The remarkable fact is that EEG tends to spontaneously organize into patterns in time and space.

The spike-wave pattern of petit mal, referenced earlier, is a classic example, but scores of others are now known. Clinical EEG practice is just recognizing characteristic EEG patterns and correlating them to specific disease states.

Fluctuating neurons

Beyond the clinic, an unsettling scientific question emerges. Simply put, how do electrical patterns arise in the brain? How do the billions of neurons and their trillions of local current flows fluctuate in just the right ways to create a globally ordered structure?

Our research group has been interested in the fundamental question of pattern formation in EEG. It turns out that activity in the brain is naturally repetitive – that is, oscillatory. This is due to the way neurons are connected and the fact that they interact by excitation and inhibition to produce push-pull effects.

Considering local oscillations as fundamental building blocks, we showed that the EEG over the entire brain could be built up from such elementary blocks. More interestingly, the differing frequencies could be made to coalesce or synchronize into a common rhythm. We recognized that synchronization of this type underlies some seizurelike patterns observed in patients.

EEG, AI, and the mind

Pattern formation in nature is deeply fascinating. How does a leopard get its spots? How does the audience at a concert spontaneously settle into a rhythmic applause? Many such questions trace their origin to a classic paper on biological patterns published in 1952. Its author was Alan Turing, better known as the father of computer science and early advocate of artificial intelligence, or AI.

The hardware underlying the majority of today's AI systems are neural networks. Neural networks were introduced in 1943 by Warren McCulloch, a physician and electroencephalographer. Like Berger, McCulloch's interest in EEG extended beyond brain disease. He wondered where in the brain's neurons and EEG lay the capacity to think. He conceived the idea of grouping artificial neuronlike computing units into networks, analogous to how real neurons in the brain are interconnected.

Together with Walter Pitts, he proved that such neural networks could function as a general-purpose computer. The seminal McCulloch-Pitts ideas were refined

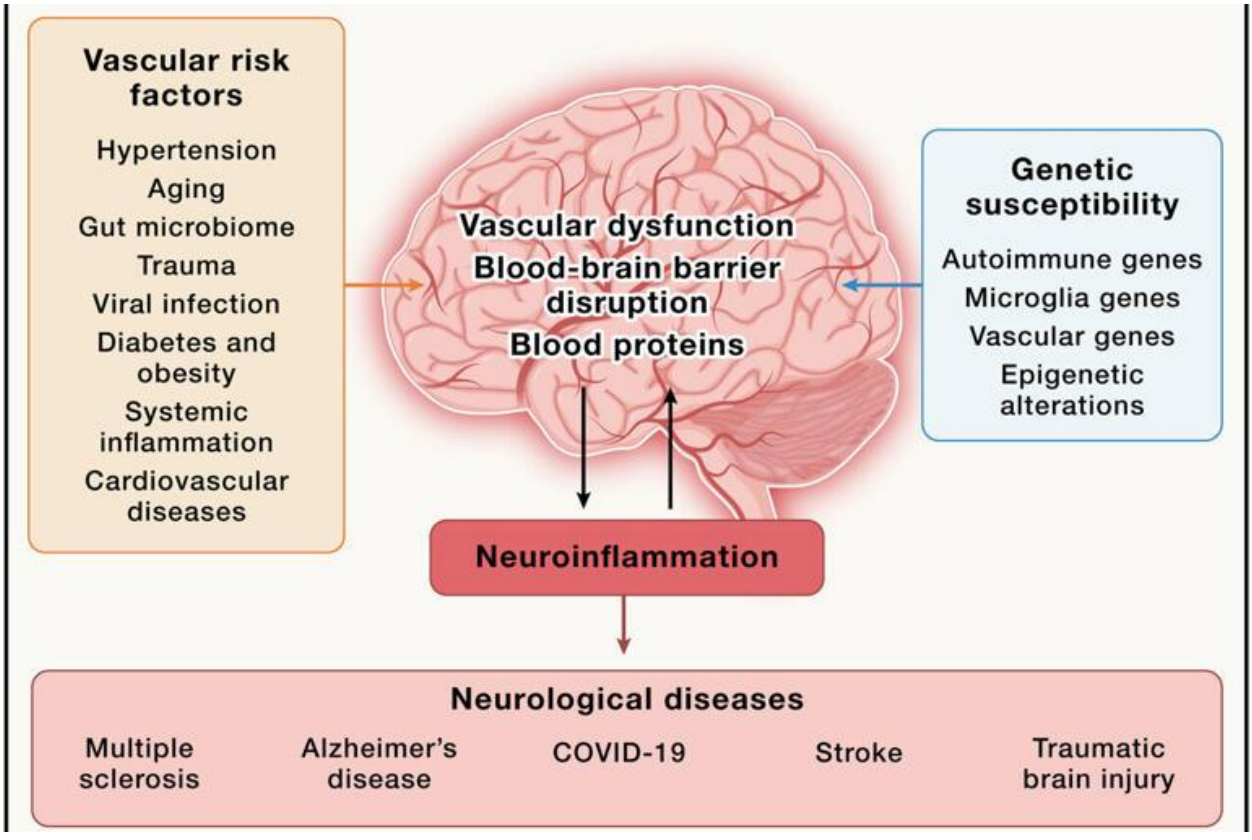
over the ensuing decades and reside in the “deep learning” neural networks of today’s AI.

Deep learning AI has infiltrated all areas of biomedicine, including neurology. For example, AI systems can successfully interpret brain scans. AI methods have also been used to analyze EEG.

Can AI systems be trained to deduce thoughts from the EEG? Can AI approach Berger’s quest for telepathy? Incredibly, recent deep-learning AI research has shown that some aspects of mental activity may be decoded from EEG.

In 2024, EEG turns 100. What windows will it open into the brain and mind in the future? Doubtless, clinical applications will grow. Surely, brain pattern generation will be better understood. Perhaps EEG will glimpse the content of the mind. And for neurologists like me surveying the AI revolution, there’s the quiet pride that EEG was really at the start of it all.

A new era of treating neurological diseases at the blood-brain-immune interface



Integration of vascular risk factors with genetic susceptibility in neurological diseases. Credit: Cell (2024). DOI: 10.1016/j.cell.2024.09.018

The question of what causes complex neurological diseases such as Alzheimer's or multiple sclerosis continues to confound scientists and doctors, with the unknowns standing in the way of early diagnoses and effective treatments.

Even among identical twins who share the same genetic risk factors, one may develop a particular neurological disease while the other does not.

That's because unlike diseases such as cystic fibrosis or sickle-cell anemia, which are caused by a single gene, most neurological disorders are associated with many—sometimes hundreds—of rare genetic variants. And on their own, these variants can't predict who will develop disease, as neurological conditions are also strongly influenced by environmental factors and vascular risks such as high blood pressure, aging, heart disease, or obesity.

But there's one often-overlooked thread that connects most neurological diseases, says Katerina Akassoglou, Ph.D., a senior investigator at Gladstone Institutes: They're marked by a toxic immune reaction caused by blood that leaks into the brain through damaged blood vessels.

"Interactions between the brain, blood vessels, and the immune system are a common thread in the development and progression of many neurological diseases that have been traditionally viewed as very different conditions," says Akassoglou, a senior investigator with the Gladstone Institute of Neurological Diseases and director of the Center for Neurovascular Brain Immunology at Gladstone and UC San Francisco. "Knowing that leaked blood is a key driver of brain inflammation, we can now approach these diseases from a different angle."

Neutralizing the culprit

Akassoglou and her lab have long investigated how blood that leaks into the brain triggers neurologic diseases, essentially by hijacking the brain's immune

system and setting off a cascade of harmful, often-irreversible effects that result in damaged neurons.

One blood protein in particular—fibrin, normally involved in blood coagulation—is responsible for setting off this detrimental cascade. The process has been observed in conditions as diverse as Alzheimer's, traumatic brain injury, multiple sclerosis, premature birth, and even COVID-19. However, Akassoglou and her team found that the process could be prevented or interrupted by "neutralizing" fibrin to deactivate its toxic properties—an approach that appears to protect against many neurological diseases when tested in animal models.

"As a first step, we know that neutralizing fibrin reduces the burden posed by vascular dysfunction," Akassoglou says. Regardless of what initially caused the blood leaks, be it a head injury, autoimmunity, genetic mutations, brain amyloid or infection, neutralizing fibrin appears to be protective in multiple animal models of disease.

The scientists previously developed a drug, a therapeutic monoclonal antibody, that specifically targets fibrin's inflammatory properties without affecting its essential role in blood coagulation. This fibrin-targeting immunotherapy has shown, in mice, to protect from multiple sclerosis and Alzheimer's, and to treat neurological effects of COVID-19. A humanized version of this first-in-class fibrin immunotherapy is already in Phase 1 safety clinical trials by Therini Bio, a biotech company launched to advance discoveries from Akassoglou's lab.

A new era of brain research

In the commentary, Akassoglou and her colleagues make the case that seemingly disparate neurological diseases must be viewed differently in light of new research on the blood-brain-immune interface.

They say that in the coming decade, scientific breakthroughs will emerge from collaborative networks of immunologists, neuroscientists, hematologists, geneticists, computer scientists, physicists, bioengineers, drug developers, and clinical researchers. These partnerships—forged across academia, industry, and

foundations—will catalyze innovation in drug discovery and transform medical practice for neurological diseases.

"This is a new opportunity for drug discovery that goes beyond addressing genes alone or environmental factors alone," Akassoglou says. "To usher in this new era, we must leverage new technologies and embrace an interdisciplinary approach that accounts for the important roles of immune and vascular systems in neurodegeneration."

More information: Katerina Akassoglou et al, Pioneering discovery and therapeutics at the brain-vascular-immune interface, *Cell* (2024). DOI: 10.1016/j.cell.2024.09.018

Provided by Gladstone Institutes

Human study provides evidence that theta phase precession supports memory formation and retrieval

Past neuroscience research has pinpointed many of the neural processes through which the human brain forms, stores and retrieves important information, such as domain-specific knowledge and memories. One dimension of human memory is the ability to link various aspects of experience to specific life events.

Past studies have suggested that this memory-related process is supported by phase precession, which is a shift in the timing at which specific neurons are fired. Up until now, however, this hypothesis had not been confirmed experimentally.

Researchers at the University of California, Davis, Harvard Medical School, Toronto Western Hospital and Cedars-Sinai Medical Center recently carried out a study aimed at probing the relationship between phase precession and memory.

Their findings, published in *Nature Human Behaviour*, suggest that theta phase precession, the shift in the time at which specific neurons fire relative to the theta rhythm in brains, contributes to memory formation and retrieval.

"Our study was inspired by previous work showing that the relative timing of spikes with respect to population activity in the form of field potentials dynamically changes as animals navigate through an environment," Jie Zheng, first author of the paper, told Medical Xpress.

"Extending this idea to human memory, the primary objective here was to test the functional role of such dynamic spike timing signals during episodic memory formation and retrieval of complex event sequences in a natural and non-spatial task."

Zheng and her colleagues recruited 22 study participants and recorded single-neuron activity and local field potentials in their medial temporal lobe as they encoded and retrieved memories from movie clips. The team embedded the movie clips with event boundaries (i.e., contextual shifts), as this allowed them to mimic the process through which humans form memories in their everyday lives.

The researchers subsequently asked participants to recall events they observed in the movie clips and the order in which they occurred. They then analyzed the single-neuron activity they recorded as the participants were both viewing the movie clips and recalling the memory of the watched clips.

"The study was conducted in patients with pharmacologically resistant epilepsy where we could concurrently record the activity of individual neurons as well as population field potential signals," said Zheng. "We observed that the precise time at which neurons fired was related to the ongoing theta rhythms inside brains and that this relative timing evolved dynamically (called phase precession)."

The experiments carried out by Zheng and her colleagues yielded very interesting results. The team observed dynamic phase precession in the brains of participants throughout the experiment, with specific neurons shifting the timing with which they fired at different stages of the experimental task.

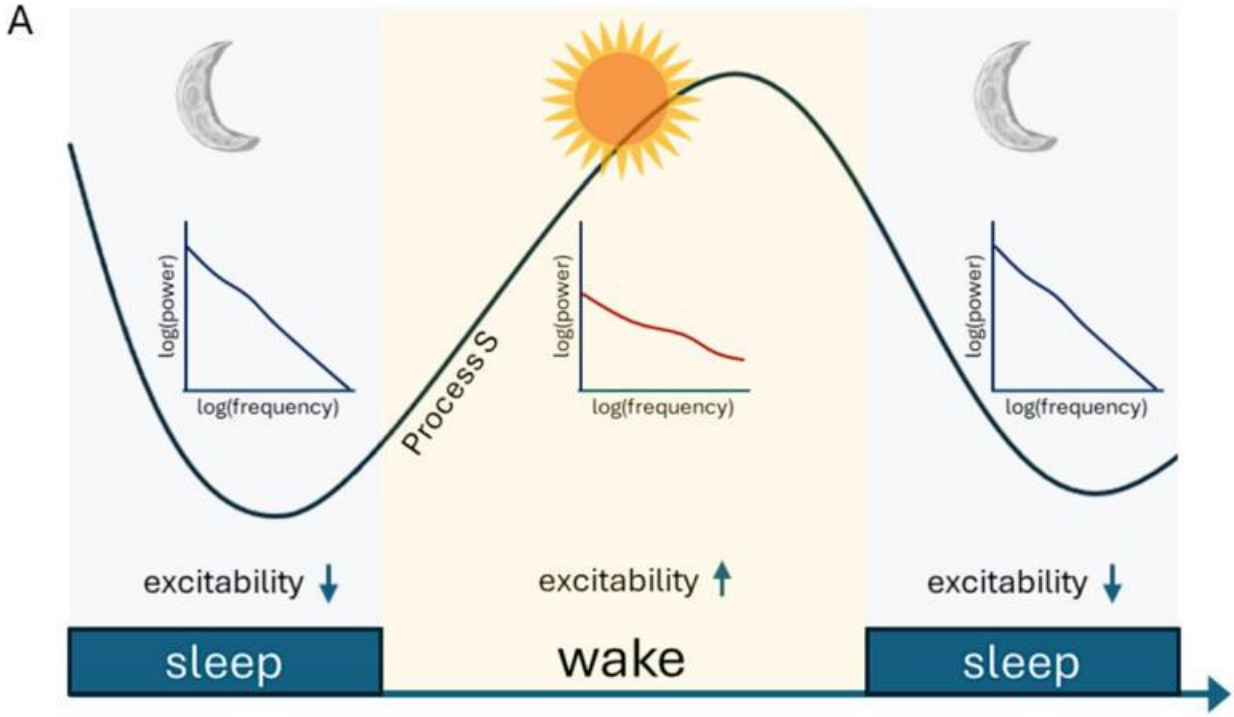
"We found strong theta phase precession at event boundaries when participants watched the clips and also when the participants answered memory questions," said Zheng. "The strength of theta phase precession was also predictive of participants' memory accuracy, especially for their order memory."

Overall, the findings of this recent study confirm the role of theta phase procession in the formation and retrieval of episodic memories. In the future, they could pave the way for further studies exploring the link between phase precession and specific memory processes.

"We would like to investigate the mechanisms underlying memory formation and retrieval of dynamic experiences with different sensory inputs (e.g., both visual and auditory), how the order of events is encoded, and how theta phase precession supports these consolidation and retrieval processes," added Zheng.

More information: Jie Zheng et al, Theta phase precession supports memory formation and retrieval of naturalistic experience in humans, *Nature Human Behaviour* (2024). DOI: 10.1038/s41562-024-01983-9

A new brain-based measure of sleepiness may provide a diagnosis in just two minutes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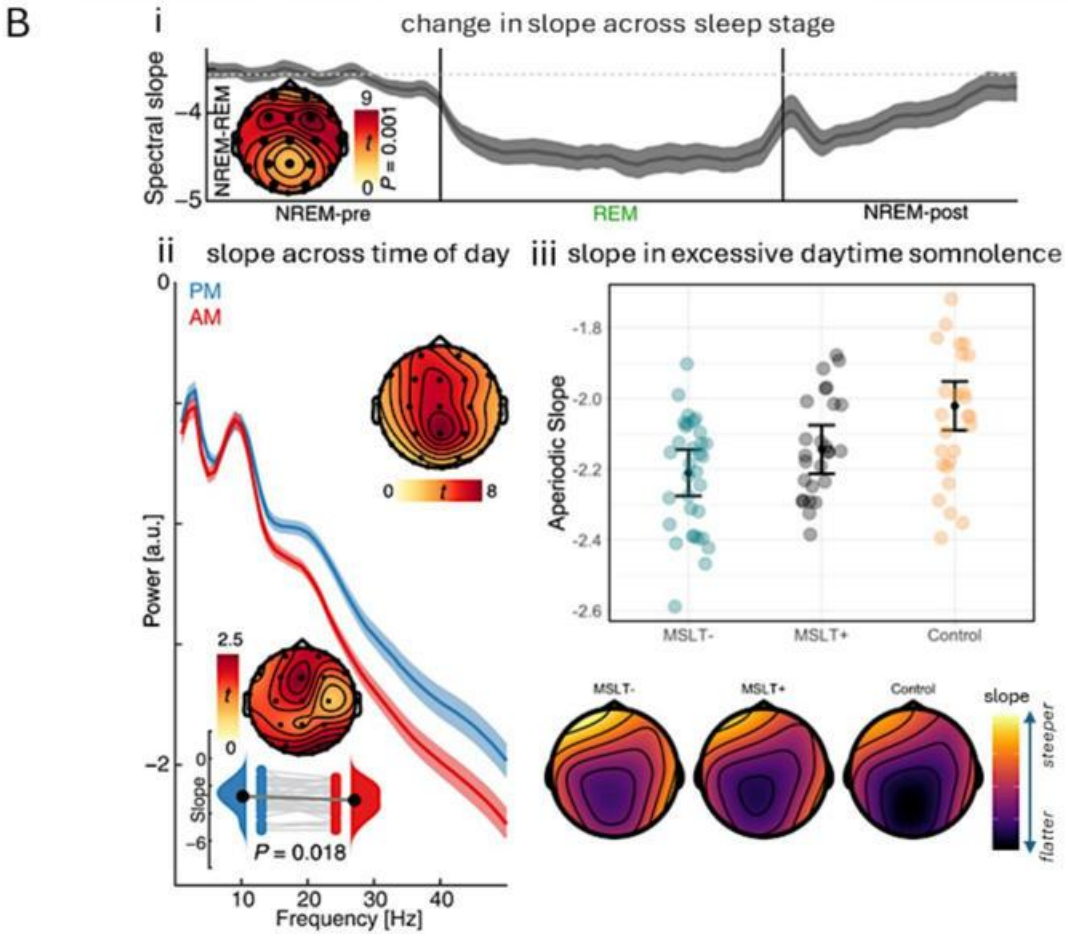
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MSLT-
MSLT+
Control
slope
steeper
flatter

Schematic overview of the relationship between the aperiodic slope and the accumulation of sleep need. Credit: Brain Research (2024). DOI: 10.1016/j.brainres.2024.149088

At some point, many of us have experienced the post-lunch sleepy hour, struggling to stay alert mid-afternoon, and reaching for the water bottle to rehydrate a tired body.

But what about those people who suffer from "excessive daytime somnolence," aka sleepiness that lasts throughout the day?

It's a recognized medical condition that is normally diagnosed by a doctor after a full-day hospital procedure, undergoing what is called the Multiple Wakefulness Test (MWT).

Now, researchers from the University of South Australia have identified a new, brain-based measure of sleepiness that may provide a diagnosis in just two minutes. Electrodes attached to the scalp in the form of an electroencephalogram (EEG) measure the electrical activity of the brain and this activity can determine the length of time it takes an individual to fall asleep.

In a separate, recent paper published in *Brain Research*, lead researcher, UniSA neuroscientist Dr. Alex Chatburn, says that using new EEG markers linked to biological processes could predict whether someone is safe enough to drive, operate machinery, or even have the mental capacity to sit an exam.

"Sleepiness is a critical biological signal that indicates the body's need for sleep, yet measuring this state in humans remains elusive," Dr. Chatburn says.

"While EEG technology has long been used to study brain activity during sleep, traditional markers face significant limitations and don't tell the whole story. They don't reflect the underlying biological processes, whereas our method tracks neuronal excitability, corresponding with the brain's sleep-wake processes."

Dr. Chatburn says the research has wide-ranging implications. "A better understanding of sleepiness could not only advance scientific knowledge, but also provide practical benefits for managing sleep disorders like insomnia, sleep apnea or other disorders where individuals experience disrupted sleep but do not feel sleepy.

"These findings could also inform workplace safety, where detecting and managing sleepiness could prevent accidents in industries that demand high levels of attention."

The team are presenting their findings at the Sleep DownUnder 2024 conference in the Gold Coast this week.

More information: Alex Chatburn et al, Considerations towards a neurobiologically-informed EEG measurement of sleepiness, *Brain Research* (2024). DOI: 10.1016/j.brainres.2024.149088

Provided by University of South Australia

Scientists discover "glue" that holds memory together in fascinating neuroscience breakthrough

A team of scientists has made a significant discovery about how the brain retains long-term memories. They identified the molecule KIBRA, which acts as a "glue" to anchor PKMζ, an enzyme critical for strengthening synaptic connections between neurons. This interaction ensures that memories are not lost as brain proteins degrade and regenerate, offering a deeper understanding of memory stability. The findings have been published in *Science Advances*.

The scientists were driven by a long-standing question in neuroscience: how can memories last for years or even decades when the molecules in our brains are constantly being replaced? Neurons store information in the strength of synapses, but the proteins and molecules in those synapses are unstable and degrade after just a few days. This creates a puzzle—if the building blocks of memory are so short-lived, what allows us to maintain long-term memories?

The idea that certain molecular interactions might provide stability to memory storage has been around since 1984, when Francis Crick proposed that continuous interactions between proteins might maintain synaptic strength over time. This new study sought to explore this hypothesis further, focusing on the

role of PKMζ and how its interaction with another molecule, KIBRA, might contribute to the stability of long-term memory.

“I have been interested in memory since I was a little boy. I also had the sense that there were always deeper, simpler levels of understanding for any mysterious process, and I was driven by curiosity to find the deepest for memory,” said study author Todd C. Sacktor, a distinguished professor at SUNY Downstate Health Sciences University.

Sacktor explained that in college, he became interested in understanding how memory is stored at the molecular level, focusing on the persistent strengthening of synapses during learning. During his neurology residency at Columbia, he worked in James Schwartz’s lab, which guided him toward discovering PKMζ, an enzyme that strengthens synaptic connections.

“The rest was simply trying to figure out what PKMζ did and how it worked,” Sacktor continued. “Ultimately, for memory to last years, i.e., beyond the lifespans of individual molecules, we realized PKMζ had to have a partner, which is the discovery presented in this paper.”

André Fenton, a professor of neural science at New York University and another of the study’s principal investigators, added that he was drawn to this research because he is interested in uncovering the fundamental processes underlying our subjective experience.

“While experience requires complex brain activity to process information, I have long thought that our concept of memory is essential to this processing, not merely for storing what has already happened but also for generating expectations and beliefs that influence, if not dictate, subsequent experience,” Fenton said. “While it has always been a fascinating problem to work out how memory can persist for years when the constituent protein components only last days to weeks, work that challenged some of our prior findings and understanding pointed to a solution.”

To explore the connection between KIBRA and PKMζ, the researchers used male laboratory mice. The scientists conducted a series of experiments involving hippocampal slices, a region of the brain critical for memory, and various techniques such as proximity ligation assays and confocal microscopy to visualize the molecular interactions between KIBRA and PKMζ.

They also used genetically modified mice lacking PKMζ to see how memory maintenance differed when this enzyme was missing. In addition, behavioral tests, such as spatial memory tasks, were used to assess the impact of disrupting the KIBRA-PKMζ interaction on memory retention.

One key experiment involved applying a drug called ζ-stat, which blocks the interaction between KIBRA and PKMζ, to see if this would disrupt the stability of synaptic potentiation and long-term memory. Another experiment introduced a peptide called K-ZAP, which mimics KIBRA's binding site and interferes with its ability to anchor PKMζ, further testing the importance of this interaction.

The study found evidence that KIBRA plays a vital role in stabilizing PKMζ at synapses, effectively creating a "persistent synaptic tag" that helps maintain long-term memory. The researchers found that when synapses are activated during learning, KIBRA binds to those synapses and helps PKMζ stay attached. This connection ensures that the synapses remain strong, even as other molecular components degrade and are replaced.

"For the first time, we have a fundamental biological understanding of how memory can last for years, perhaps even decades," Sacktor told PsyPost.

Memories are stored by the interaction of two proteins: a structural protein, KIBRA (green), that acts as a persistent synaptic tag, and a synapse-strengthening enzyme, protein kinase Mzeta (red). Drugs that disrupt the memory-perpetuating interaction (other colors) erase pre-established long-term and remote memories. (Credit: Changchi Hsieh)© PsyPost

More specifically, they observed that when ζ-stat was used to block the KIBRA-PKMζ interaction, it reversed the potentiation of synapses that had previously been strengthened during learning. This effect was selective, impacting only the activated synapses that were involved in memory formation, while leaving unactivated synapses unaffected. This indicates that the KIBRA-PKMζ interaction is crucial for maintaining the strength of memory-related synapses.

In behavioral tests, disrupting the KIBRA-PKMζ interaction in mice also led to a loss of long-term memory. Mice that received ζ-stat injections after learning a spatial memory task were unable to recall the location of a shock zone in subsequent tests. Interestingly, this effect was not seen in genetically modified mice that lacked PKMζ, further confirming that KIBRA's interaction with PKMζ is essential for memory maintenance.

The researchers also found that this molecular interaction is not just important for short-term memory, but can maintain memory for weeks. Even when PKMζ was degraded over time, the KIBRA-PKMζ complexes remained at the synapses, suggesting that new PKMζ molecules continue to be synthesized and incorporated into the same synaptic locations, allowing memories to persist long after the initial learning.

“The persistent KIBRA-PKMζ interaction explains how memory can last for a lifetime, something humans have been trying to understand for a very long time, at least since Plato wrote about it,” Fenton said.

“But there’s more if we connect some dots. A human brain is made up of about 100 billion neurons, each of which receives input connections at synapses from about 10 thousand other neurons. When we have any experience we use the neural circuits of our brain to process information defined by the flow of electrochemical activity through subnetworks of those connections between millions of neurons. Memory may be the result of experience changing those connections, typically a very small (1%) subset. How does an experience today persistently change connections so memory of the experience last years?”

“Our work determined that memory is the result of an active, ongoing biochemical process in which the kinase action of a persistently active catalyst protein, PKMζ is targeted to the experience-activated connections within the neurons that constitute the information processing connections of the experience-mediating neural circuit,” Fenton explained. “PKMζ is generated in an activated neuron and because KIBRA, a targeting molecule accumulates at the activated connections, it directs the kinase action of PKMζ to those specific locations.

“The KIBRA-PKMζ interaction persists because the KIBRA-PKMζ complex is more stable than the individual protein components and like the paradox of Theseus’ ship persisting despite all the planks being replaced, the KIBRA-PKMζ complex persists even though the individual protein components are continually replaced.”

“The takeaway is that experience activates neural circuits that process information and that processing creates memory, which depends on an elegant continually active biophysical process, which at once stores information and by storing that information also changes the neural circuit and with it the information processing

within which future experience will occur," Fenton told PsyPost. "Memory is about the future."

Although the study offers strong evidence that KIBRA is crucial for sustaining long-term memory by stabilizing PKMζ at synapses, certain limitations remain. The researchers acknowledge that not all forms of memory may rely on this molecular interaction. For example, the study found that some types of memory, such as contextual fear memory, are maintained through PKMζ-independent mechanisms. Understanding how these different systems operate will require further investigation.

"There are some memories that are not stored by PKMζ," Sacktor noted. "Does KIBRA play a role in these by interacting with a different, but related synapse-strengthening molecules, or is there completely different mechanisms?"

Another limitation is that while KIBRA helps explain how memories can last for years despite molecular turnover, the study did not fully explain how the process of memory formation begins—specifically, how KIBRA is initially recruited to the synapses involved in memory formation. This will be an important area for future research.

The researchers also plan to explore the potential applications of their findings for treating memory-related disorders. Since the KIBRA-PKMζ interaction is so critical for memory stability, drugs that target this process could potentially be used to enhance memory in conditions like Alzheimer's disease or to weaken harmful memories in conditions like post-traumatic stress disorder.

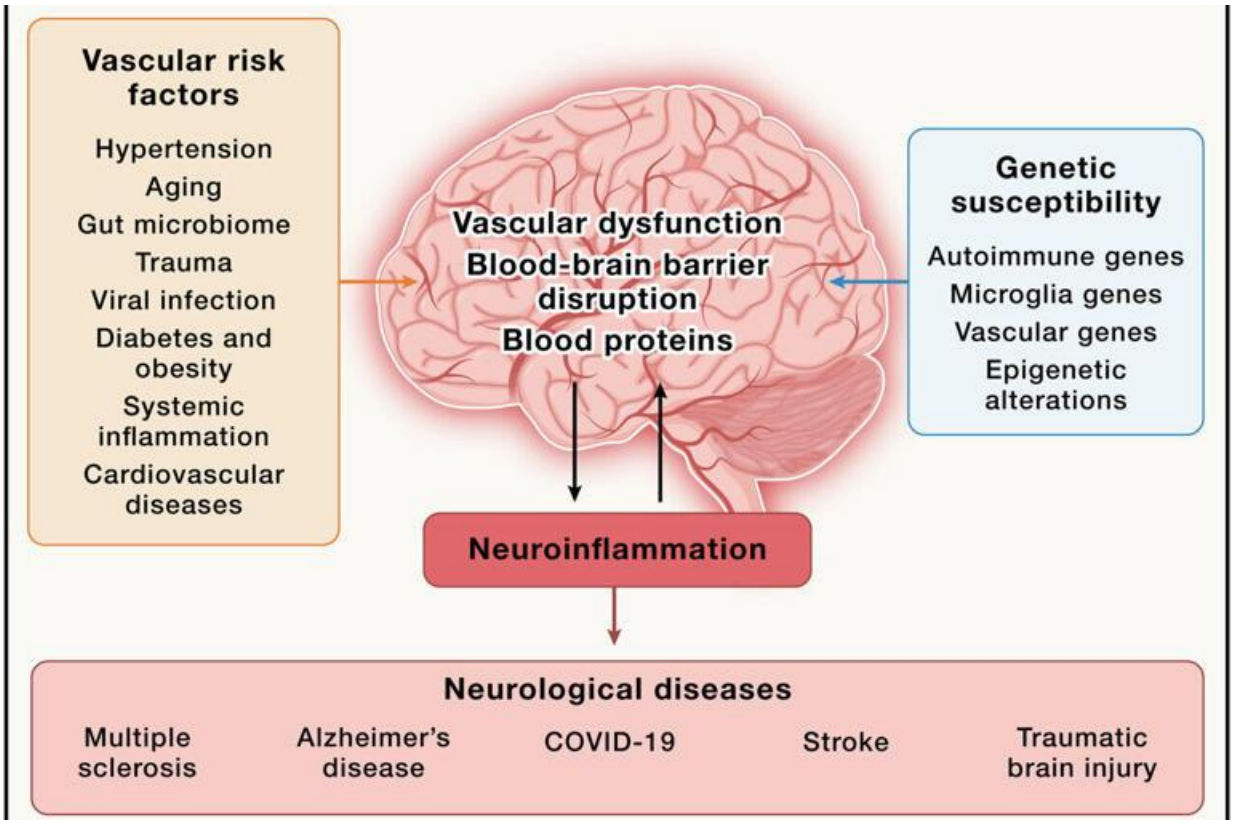
"We wish to explain how the process of memory persistence is initiated," Fenton said. "In other words, how does the KIBRA appear and accumulate; how are the memory-changed connections arranged within a neuron and between neurons; how specifically does the KIBRA-PKMζ mediated change in connections change information processing; and how can this fundamental neurobiology be used to improve outcomes in disorders like Alzheimer's disease, and mental illness?"

"In any fundamental discovery in biology, there will be 'low-lying fruit' in medicine—diseases that can now be treated," Sacktor said. "Often which diseases cannot be predicted ahead of time. I am curious which psychiatric or neurological diseases it will be for the discovery of KIBRA-PKMζ's role in memory."

“Doing this work is painstakingly slow and careful, and at times frustrating but has always been joyous!” Fenton added.

The study, “KIBRA anchoring the action of PKMζ maintains the persistence of memory,” was authored by Panayiotis Tsokas, Changchi Hsieh, Rafael E. Flores-Obando, Matteo Bernabo, Andrew Tcherepanov, A. Iván Hernández, Christian Thomas, Peter J. Bergold, James E. Cottrell, Joachim Kremerskothen, Harel Z. Shouval, Karim Nader, André A. Fenton, and Todd C. Sacktor.

A new era of treating neurological diseases at the blood-brain-immune interface



Integration of vascular risk factors with genetic susceptibility in neurological diseases. Credit: Cell (2024). DOI: 10.1016/j.cell.2024.09.018

The question of what causes complex neurological diseases such as Alzheimer's or multiple sclerosis continues to confound scientists and doctors, with the unknowns standing in the way of early diagnoses and effective treatments.

Even among identical twins who share the same genetic risk factors, one may develop a particular neurological disease while the other does not.

That's because unlike diseases such as cystic fibrosis or sickle-cell anemia, which are caused by a single gene, most neurological disorders are associated with many—sometimes hundreds—of rare genetic variants. And on their own, these variants can't predict who will develop disease, as neurological conditions are also strongly influenced by environmental factors and vascular risks such as high blood pressure, aging, heart disease, or obesity.

But there's one often-overlooked thread that connects most neurological diseases, says Katerina Akassoglou, Ph.D., a senior investigator at Gladstone Institutes: They're marked by a toxic immune reaction caused by blood that leaks into the brain through damaged blood vessels.

"Interactions between the brain, blood vessels, and the immune system are a common thread in the development and progression of many neurological diseases that have been traditionally viewed as very different conditions," says Akassoglou, a senior investigator with the Gladstone Institute of Neurological Diseases and director of the Center for Neurovascular Brain Immunology at Gladstone and UC San Francisco. "Knowing that leaked blood is a key driver of brain inflammation, we can now approach these diseases from a different angle."

Neutralizing the culprit

Akassoglou and her lab have long investigated how blood that leaks into the brain triggers neurologic diseases, essentially by hijacking the brain's immune system and setting off a cascade of harmful, often-irreversible effects that result in damaged neurons.

One blood protein in particular—fibrin, normally involved in blood coagulation—is responsible for setting off this detrimental cascade. The process has been observed in conditions as diverse as Alzheimer's, traumatic brain injury, multiple sclerosis, premature birth, and even COVID-19. However, Akassoglou and her team found that the process could be prevented or interrupted by "neutralizing" fibrin to deactivate its toxic properties—an approach that appears to protect against many neurological diseases when tested in animal models.

"As a first step, we know that neutralizing fibrin reduces the burden posed by vascular dysfunction," Akassoglou says. Regardless of what initially caused the blood leaks, be it a head injury, autoimmunity, genetic mutations, brain amyloid or infection, neutralizing fibrin appears to be protective in multiple animal models of disease.

The scientists previously developed a drug, a therapeutic monoclonal antibody, that specifically targets fibrin's inflammatory properties without affecting its essential role in blood coagulation. This fibrin-targeting immunotherapy has shown, in mice, to protect from multiple sclerosis and Alzheimer's, and to treat neurological effects of COVID-19. A humanized version of this first-in-class fibrin immunotherapy is already in Phase 1 safety clinical trials by Therini Bio, a biotech company launched to advance discoveries from Akassoglou's lab.

A new era of brain research

In the commentary, Akassoglou and her colleagues make the case that seemingly disparate neurological diseases must be viewed differently in light of new research on the blood-brain-immune interface.

They say that in the coming decade, scientific breakthroughs will emerge from collaborative networks of immunologists, neuroscientists, hematologists, geneticists, computer scientists, physicists, bioengineers, drug developers, and clinical researchers. These partnerships—forged across academia, industry, and foundations—will catalyze innovation in drug discovery and transform medical practice for neurological diseases.

"This is a new opportunity for drug discovery that goes beyond addressing genes alone or environmental factors alone," Akassoglou says. "To usher in this new era, we must leverage new technologies and embrace an interdisciplinary approach that accounts for the important roles of immune and vascular systems in neurodegeneration."

More information: Katerina Akassoglou et al, Pioneering discovery and therapeutics at the brain-vascular-immune interface, *Cell* (2024). DOI: 10.1016/j.cell.2024.09.018

Provided by Gladstone Institutes

How the inflamed brain becomes disconnected after a stroke

Whether reeling from a sudden stroke or buckling under the sustained assault of Alzheimer's, the brain becomes inflamed, leading to cognitive problems and even death.

Scientists have known for many years that severe inflammation can kill the brain's neurons. Now, researchers at UC San Francisco have discovered that even subtle inflammation damages the brain.

Instead of killing neurons outright, however, relatively mild inflammation only destroys the arm-like projections, called neurites, that wire neurons together. These connections are vital for everything the brain does, including learning and memory.

Ray Swanson's team discovered that inflammation—a consequence of diseases like Alzheimer's and stroke—destroys these wires but spares the neurons. Credit: Swanson Lab/University of California, San Francisco© Provided by Medical Xpress

The findings, published last month in *Cell Reports*, describe in detail a new degenerative pathway that scientists can now try to disrupt. This could help stem the damage from common neurological diseases.

"There are several exciting drugs now entering clinical use that interrupt these inflammatory processes, and now we know to look at their effects on neurites," said Raymond Swanson, MD, senior author on the paper and a professor of neurology with joint appointments at UCSF and the San Francisco Veterans Affairs Medical Center. "Not too far off, this could have a big impact on helping our patients."

Swanson's team wanted to know how this inflammatory process was damaging the brain. They were particularly interested in molecular aggregates, called cofilactin rods (CARs), that appear after a stroke. CARs form when two proteins, called cofilin and actin, that normally maintain neurites, break loose, forming messy clumps.

CARs are known to form in response to a chemical called superoxide, which immune cells release when the brain is inflamed.

Connecting the dots from inflammation to dysfunction

To get a closer look at this process, the researchers stimulated inflammation in a part of the mouse brain that controls movement. They expected that neurons would die and the mice would have trouble moving.

The mice did struggle to move, but when the researchers looked at their brain tissue under a microscope, they were surprised to see that only the neurites had withered away, leaving the neurons isolated like stars in the night sky. The loss of these connections was enough to rob the mice of some of their motor coordination.

The scientists then tried reducing the amount of either superoxide or cofilin, and treated the brain with the same inflammatory substance. Under these conditions, fewer CARs formed, and the neurites survived. The mice also retained their coordination.

They had discovered a new pathway: inflammation caused immune cells to release superoxide, pulling cofilin and actin out of neurites and making CARs. Neurites died, and the disconnected brain malfunctioned.

A new target for treating neurodegeneration

Many neurological diseases involve inflammation, including multiple sclerosis, traumatic brain injury, and amyotrophic lateral sclerosis (ALS).

Now that scientists understand it better, they can design therapies to interrupt this inflammatory pathway. Stroke patients, for example, could be treated early on with anti-inflammatory agents to shield neurites from damage and preserve cognition.

"Particularly in the aging brain, inflammation can be harmful," Swanson said. "By homing in on how neurites are so vulnerable to inflammation, we may be able to finally gain the upper hand against some of the most common neurological diseases."

More information: Gökhan Uruk et al, Cofilactin rod formation mediates inflammation-induced neurite degeneration, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.113914

Provided by University of California, San Francisco

Activating One Specific Brain Cell Extended Lifespan in Mice by 70 Days

Aging might have advantages in wisdom, experience, and even evolution, but the gradual breakdown of biology that comes with growing old is rarely much fun for anybody.

A new study in mice suggests it may not always have to be this way.

"We demonstrated a way to delay aging and extend healthy lifespans in mice by manipulating an important part of the brain," says Washington University developmental biologist Shin-ichiro Imai.

Our brains control a vast number of bodily functions, primarily by way of nervous impulses, which can manage communication networks based on the ebb and flow of hormones.

The infrastructure carrying these communication signals and their surroundings deteriorate as we age, causing increasing faults.

So our organs and tissues start to miss out on signals needed to maintain themselves.

Signaling chemicals that form parts of the pathway between our brains and fat tissues, specifically white adipose fat, have been associated with aging in mice previously, so Imai and colleagues took a closer look at the critical early steps in this communication network.

They allowed one group of rodents to age naturally while tweaking the neurons at the beginning of the brain to fat pathway so they remained active. These cells, DMHPpp1r17, are tucked away in our brain's hypothalamus, an important conduit between our nervous system and the body's hormone system.

Incredibly, the mice that received the neuron activation treatment lived 60 to 70 days longer than the control mice, who died within the typical laboratory mouse lifespan of about 1,000 days.

More importantly, the mice that underwent neural treatment had thicker, shinier coats and were more active during their old age, suggesting they were healthier for longer too.

Further investigation revealed parts of the mechanism at play.

When the DMHPpp1r17 neurons are on, they can activate our body's fight or flight response – our sympathetic nervous system using the Ppp1r17 molecule. This promotes the use of our body's white adipose stores that release a protein called eNAMPT, which in turn regulates hypothalamus neurons, completing the circuit.

"Ppp1r17 is also well conserved in various vertebrate species such as human, chimpanzee, monkey, rat, mouse, bovine, rabbit, chicken, xenopus, and zebra finch, suggesting that Ppp1r17 carries some essential functions throughout evolution," the researchers explain in their paper.

This is a vital circuit for fueling our bodies, but the normal aging mice started producing less Ppp1r17, activating fewer fat stores.

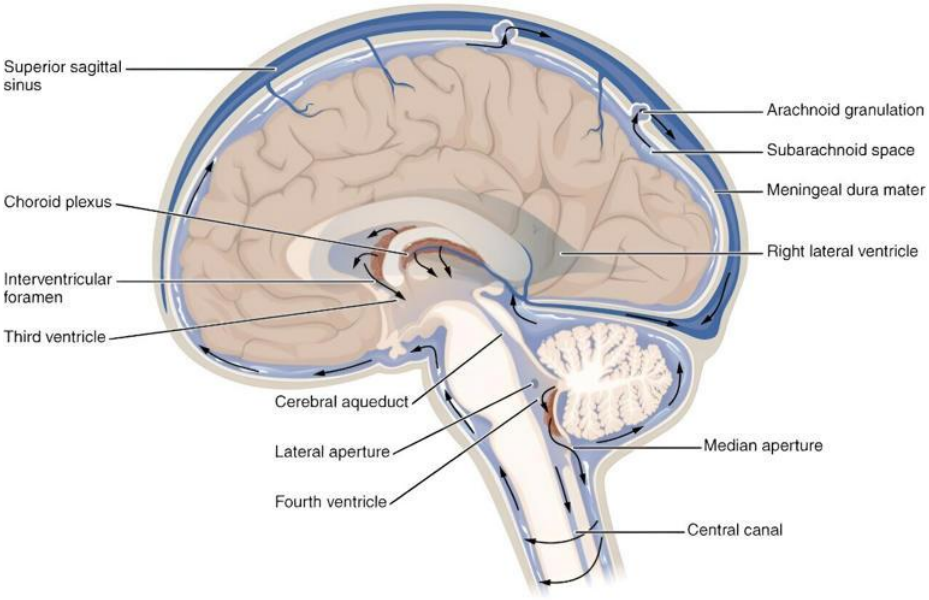
With less activity, the nerves through our adipose tissues begin to degrade, meaning even less eNAMPT is produced, so even fewer hypothalamus neurons are activated, creating a self-propagating system of deterioration.

There are still many details to hash out, including if eNAMPT works directly on the hypothalamic neurons or if there are more intermediary steps. The team is also keen to discover if this feedback loop influences communication between other tissue types within our bodies, like skeletal muscle.

If so, this could explain an awful lot, as many known factors of biological aging, including stress and stress mitigators, weight, and exercise, all influence some part of this brain to fat system – another example of just how physiologically linked we are to the world around us.

This research was published in *Cell Metabolism*.

Fluid keeps your brain from crushing itself and shields your spine from shock—what happens when it stops working



Cerebrospinal fluid circulates throughout the brain and spinal cord. Credit: OpenStax, CC BY-SA

Cerebrospinal fluid, or CSF, is a clear, colorless liquid that plays a crucial role in maintaining the health and function of your central nervous system. It cushions the brain and spinal cord, provides nutrients and removes waste products.

Despite its importance, problems related to CSF often go unnoticed until something goes wrong.

I am a neurologist and headache specialist. In my work treating patients with CSF pressure disorders, I have seen these conditions present in many different ways. Here's what happens when your cerebrospinal fluid stops working:

What is cerebrospinal fluid?

CBF is made of water, proteins, sugar, ions and neurotransmitters. It is primarily produced by a network of cells called the choroid plexus, which is located in the brain's ventricles, or cavities.

The choroid plexus produces approximately 500 milliliters of CSF daily, but only about 150 milliliters are present within the central nervous system at any given time due to constant absorption and replenishment in the brain. This fluid circulates through the ventricles of the brain, the central canal of the spinal cord and the subarachnoid space surrounding the brain and spinal cord.

CSF has several critical functions. It protects the brain and spinal cord from injury by absorbing shocks. Suspending the brain in this fluid reduces its effective weight and prevents it from being crushed under its own mass. Additionally, CSF helps maintain a stable chemical environment in the central nervous system, facilitating the removal of metabolic waste and the distribution of nutrients and hormones.

When the production, circulation or absorption of cerebrospinal fluid is disrupted, this can lead to significant health issues. Two notable conditions are CSF leaks and idiopathic intracranial hypertension.

CSF leak

A CSF leak occurs when the fluid escapes through a tear or hole in the dura mater—the tough, outermost layer of the meninges that surrounds the brain and spinal cord.

The dura can be damaged from head injuries or be punctured during surgical procedures involving the sinuses, brain or spine, such as lumbar puncture, epidurals, spinal anesthesia or myelogram. Spontaneous CSF leaks can also occur without any identifiable cause.

CSF leaks were originally thought to be relatively rare, with an estimated annual incidence of 5 per 100,000 people. However, with increased awareness and advances in imaging, health care providers are discovering more and more leaks. They tend to occur more frequently in middle-aged adults and are more common in women than men.

Risk factors for the condition include connective tissue disorders such as Ehlers-Danlos syndrome as well as postural orthostatic tachycardia syndrome.

Unfortunately, it's common for health care providers to misdiagnose a CSF leak as another condition, like migraine, sinus infections or allergies. What can make diagnosing a CSF leak challenging is its broad symptoms. Most people with CSF leak have a positional headache that improves when lying down and worsens when standing. Pain is usually felt in the back of the head and may involve the neck and between the shoulder blades. In addition to headaches, patients may experience ringing in the ears, vision disturbances, memory problems, brain fog, dizziness and nausea.

Imaging may help guide diagnosis, including an MRI of your brain or entire spine, or a myelogram of the space surrounding your spinal cord. Features of a CSF leak that are visible in a scan include your brain sagging down in the base of your skull as well as a fluid collection outside of your dura. However, an estimated 19% of people with a CSF leak can have normal scans, so not seeing signs of a leak on imaging does not entirely rule it out.

Conservative treatment for a CSF leak involves rest, lying flat and increasing your fluid intake to give your spine time to heal the puncture. Increasing your caffeine

consumption to an equivalent of three to four cups of coffee per day can also help by increasing CSF production through stimulating the choroid plexus. Caffeine also relieves pain by interacting with adenosine receptors, which are key players in the body's pain perception mechanisms.

If a conservative approach is not successful, an epidural blood patch may be necessary. In this procedure, blood is drawn from your arm and injected into your spine. The injected blood can help form a covering over the hole and promote the healing process. Headache improvement can be fast, but if the patch does not work or the results are short-lived, additional testing may be needed to better locate the site of the leak. In rare cases, surgery may be recommended. Most patients with CSF leak respond to some form of these treatments.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension is a disorder involving an excess of CSF that elevates pressure inside the skull and compresses the brain. The term "idiopathic" indicates that the cause of the raised pressure is unknown.

Most patients with idiopathic intracranial hypertension have a history of obesity or recent weight gain. Other risk factors include taking certain medications such as tetracycline, excessive vitamin A, tretinoin, steroids and growth hormone. Middle-aged obese women are 20 times more likely to be diagnosed with idiopathic intracranial hypertension than other patient groups. As obesity becomes more prevalent, so too does the incidence of this condition.

Patients with idiopathic intracranial hypertension typically experience headaches and vision changes, tinnitus or eye pain. Papilledema, or swelling of the optic disk, is the hallmark finding on a fundoscopic examination of the back of the eye. Clinicians may also observe paralysis of the patient's eye muscles.

Brain imaging of patients suspected of having idiopathic intracranial hypertension is crucial to excluding other causes of elevated CSF pressure, such as brain tumors or blood clots in the brain. A lumbar puncture or spinal tap to measure the pressure and composition of CSF is also central to diagnosis.

Since high intracranial pressure can damage the optic nerve and lead to permanent vision loss, the primary goal of treatment is to decrease pressure and preserve the optic nerve. Treatment options include weight loss, dietary changes and medications to reduce CSF production. Surgical procedures can also reduce intracranial pressure.

Future directions and unknowns

Cerebrospinal fluid is indispensable for brain health. Despite advancements in understanding diseases related to CSF, several aspects remain unclear.

The exact mechanisms that lead to conditions like CSF leaks and idiopathic intracranial hypertension are not fully understood, though there are many theories. Further research is vital to enhance diagnostic accuracy and effective treatments for CSF disorders.

Scientists show how shallow learning mechanism used by the brain can compete with deep learning

Neural network learning techniques stem from the dynamics of the brain.

However, these two scenarios, brain learning and deep learning, are intrinsically different. One of the most prominent differences is the number of layers each one possesses.

Deep learning architectures typically consist of numerous layers that can be increased to hundreds, enabling efficient learning of complex classification tasks. Contrastingly, the brain consists of very few layers, yet despite its shallow architecture and noisy and slow dynamics, it can efficiently perform complex classification tasks.

The critical question driving new research is the possible mechanism underlying the brain's efficient shallow learning, enabling it to perform classification tasks with the same accuracy as deep learning. In an article published in *Physica A: Statistical Mechanics and its Applications*, researchers from Bar-Ilan University in Israel show how such shallow learning mechanisms can compete with deep learning.

"Instead of a deep architecture, like a skyscraper, the brain consists of a wide shallow architecture, more like a very wide building with only very few floors," said Prof. Ido Kanter of Bar-Ilan's Department of Physics and Gonda (Goldschmied) Multidisciplinary Brain Research Center, who led the research.

"The capability to correctly classify objects increases where the architecture becomes deeper, with more layers. In contrast, the brain's shallow mechanism indicates that a wider network better classifies objects," said Ronit Gross, an undergraduate student and one of the key contributors to this work. "Wider and higher architectures represent two complementary mechanisms," she added.

Nevertheless, the realization of very wide shallow architectures, imitating the brain's dynamics, requires a shift in the properties of advanced GPU technology, which is capable of accelerating deep architecture, but fails in the implementation of wide shallow ones.

More information: Ofek Tevet et al, Efficient shallow learning mechanism as an alternative to deep learning, *Physica A: Statistical Mechanics and its Applications* (2024). DOI: 10.1016/j.physa.2024.129513

Provided by Bar-Ilan University

New state of mind: Rethinking how researchers understand brain activity.

Understanding the link between brain activity and behavior is among the core interests of neuroscience. Having a better grasp of this relationship will both help scientists understand how the brain works on a basic level and uncover what specifically goes awry in cases of neurological and psychological disease.

One way that researchers study this connection is through what are known as "brain states," patterns of neural activity or connectivity that emerge during specific cognitive tasks and are common enough in all individuals that they become predictable. Another, newer, approach is the study of brain waves, rhythmic, repetitive patterns of brain cell activity caused by synchronization across cells.

In a new paper, two Yale researchers propose that these two ways of thinking about brain activity may not represent separate events but two aspects of the same occurrence. Essentially, they suggest that though brain states are traditionally thought of as a snapshot of brain activity while waves are more like a movie, they're capturing parts of the same story.

Reconsidering these two approaches in this context, the researchers say, could help both fields benefit from the methods and knowledge of the other and advance our understanding of the brain.

Inspired by ecological, conservation, and Indigenous philosophies, Maya Foster, a third-year Ph.D. student in the Department of Biomedical Engineering, began pursuing this idea once she joined the lab of Dustin Scheinost, an associate professor in the Department of Radiology and Biomedical Imaging at Yale School of Medicine.

They are co-authors of the new paper, published in the journal *Trends in Cognitive Sciences*.

"We're arguing that rather than a brain state being one single thing, it's a collection of things, a collection of discrete patterns that emerge in time in a predictable way," she said.

In an interview with Yale News, Foster and Scheinost describe their proposal, and discuss how they might help researchers better understand the mysteries of the brain. This interview has been edited and condensed.

When did you start to consider these might be two aspects of the same occurrence?

Maya Foster: This has been on my mind even before I came to this lab. I was reading a book—"Erosion: Essays of Undoing" by Terry Tempest Williams—and she talks about how human-made machinery like helicopters cause vibrations that interrupt the natural pulse of things and cause things like rock formations to fall apart. Relatedly, there are a lot of Indigenous populations that believe everything has a pulse. And that got me thinking of the brain and whether we have some type of resonance or vibration that can be disrupted.

Then I joined this lab and Dustin let me experiment with a lot of different things. During one of those experiments, I input some data into a particular analysis and the outputs looked wave-like, and patterns emerged and then repeated. That took me down a whole rabbit hole of research literature and there was a lot of evidence for this idea of wave-like patterns in brain states.

What are the benefits of considering brain states as wave-like?

Foster: I think it creates a synergy where both sides—the brain state folks and the brain wave folks—benefit by learning from each other. And maybe the gaps in knowledge we have now when it comes to how brain activity relates to behavior might be filled by both groups working together.

Dustin Scheinost: Brain waves are newer in this field and they're complex. And any time you can take something new and relate it to something old—brain states in this case—it gives you a natural jumping off point. You can bring along everything you've learned so far. It's kind of like not throwing the baby out with the bath water. We don't need to drop brain states. They've informed us, but we can go in a different direction with them too.

How are you proposing researchers consider brain states and brain waves now?

Foster: Borrowing from physics, when you analyze light, it can be a discrete point—a photon—or it can be wave-like. And that's one way we're thinking about this. Similarly, depending on how you analyze brain states you can get static patterns, much like a photon, or you if you look at activity more dynamically, certain patterns start to occur more than once over time, kind of like a wave.

So we're arguing that rather than a brain state being one single thing, it's a collection of things, a collection of discrete patterns that emerge in time in a predictable way.

For example, if we measured four distinct patterns in brain activity as someone completed a cognitive task, a brain state could be that pattern one emerges, then pattern three, then two, then four, and that series might repeat over time. And when that repetition stops, that would be the end of that particular brain state.

You also draw comparisons to the musical technique known as 'fugue.' How does that fit with how you're visualizing these phenomena?

Foster: I'm a music person, so that's where this came from. In a fugue, you have a basic melody and then that melody emerges later in the music in different forms and formats. For instance, the melody will play, then some other music comes in, then the melody returns with the same rhythm and time sequence but maybe it's in a different key.

Fugues are cyclical and wave-like, they have distinct groups of notes, and there's a systematic repetition and sometimes layering of the main melody. We're arguing that brain states are also wave-like, have distinct patterns of brain activity, and display systematic repetition and layering of sequential patterns.

How are you hoping other researchers respond to your argument?

Foster: I would love feedback, honestly. There is evidence for what we're proposing but when it comes to implementing these ideas going forward, it would be helpful to have a conversation about how that might work. There are a lot of different strategies and I'm interested in a broader conversation about how we as researchers might go about studying this.

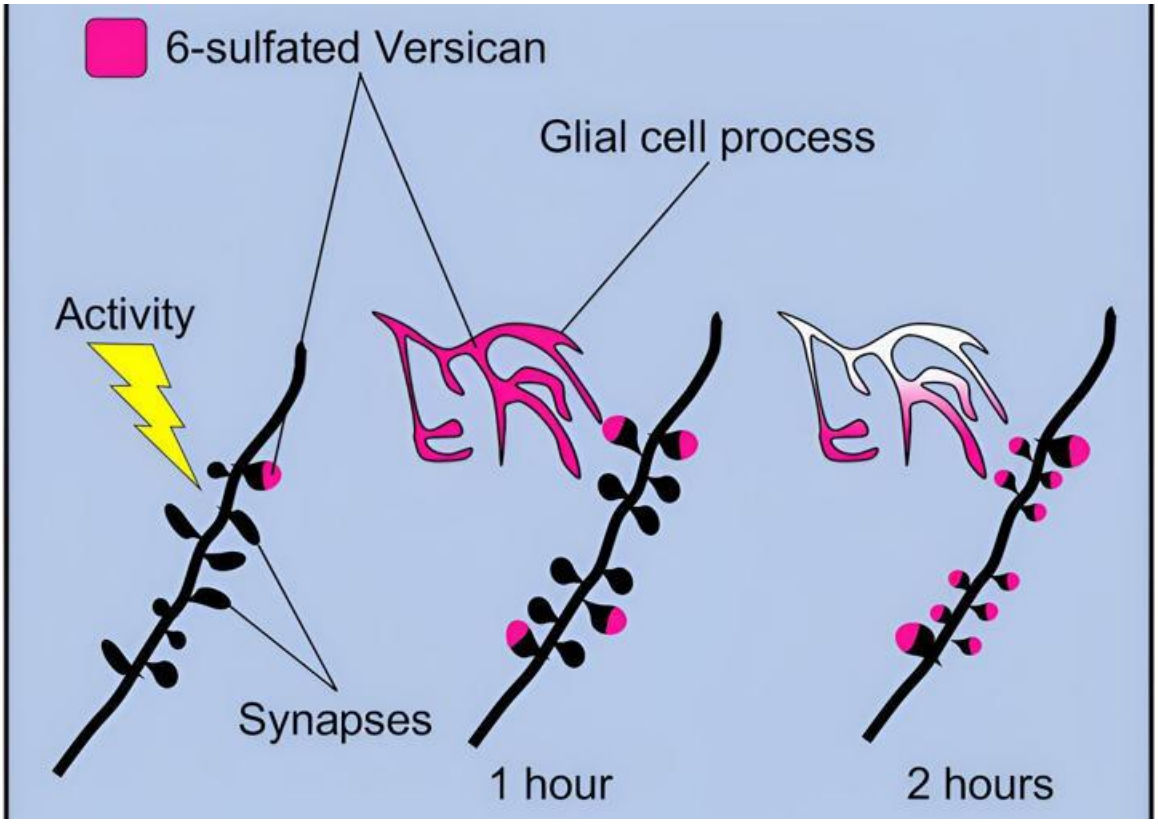
What's it like as someone who has been in this field for a while to have a student come in with a new idea like this?

Scheinost: You can get set in your ways as a researcher and you need new ideas, new creativity. Sometimes they may sound outlandish when you first hear them. But then you ruminate, and they start to take form. And it's fun. That's really where the fun of this job is, to hear new ideas and see how people discuss and debate them.

More information: Maya Foster et al, Brain states as wave-like motifs, *Trends in Cognitive Sciences* (2024). DOI: 10.1016/j.tics.2024.03.004

Provided by Yale University

Researchers demonstrate a new mechanism of neural plasticity underlying learning and memory processes



Graphical abstract. Credit: Cell Reports (2024). DOI: 10.1016/j.celrep.2024.114112© Provided by Medical Xpress

Neurons are important, but they are not everything. Indeed, it is "cartilage," in the form of clusters of extracellular matrix molecules called chondroitin sulfates, located in the outside nerve cells, that plays a crucial role in the brain's ability to acquire and store information.

A study published in *Cell Reports* describes a new mechanism of brain plasticity, or how nerve connections change in response to external stimuli. The paper is

titled "Focal clusters of peri-synaptic matrix contribute to activity-dependent plasticity and memory in mice."

The work stems from a collaboration between the Harvard Medical School, the University of Trento, and the German Center for Neurodegenerative Diseases (DZNE) in Magdeburg.

"Sensory skills and the ability to understand our surroundings depend on the activity of the brain, which enables us to perceive and process stimuli that come from the outside world. Through our brains we are able to acquire and store new information, and to remember information we have already acquired," say Yuri Bozzi and Gabriele Chelini.

"This fascinating phenomenon is made possible by the brain's ability to continuously change the structure and effectiveness of neuronal connections (synapses) in response to external stimuli. An ability that goes by the name of synaptic plasticity. Understanding how synaptic modifications occur and how they contribute to learning and memory is one of the great challenges in neuroscience."

Yuri Bozzi is a professor at the University of Trento and co-senior author. Gabriele Chelini is the first author of the study. Chelini worked on this project starting in 2017, as a postdoctoral fellow in a lab directed by Sabina Berretta (McLean Hospital and Harvard Medical School, Boston), and completed the scientific publication during his years as a postdoctoral fellow in Bozzi's lab at the University of Trento.

At the center of the research are chondroitin sulfates, molecules well known for their role in joints, which also play a crucial function in brain plasticity, being an integral part of the brain's extracellular matrix, as was originally discovered in 2001 by Dr. Alexander Dityatev's group.

In 2007, a Japanese study described the presence of clusters of chondroitin sulfates, circular in shape, scattered seemingly randomly in the brain. This work had slipped into oblivion, however, until Sabina Berretta's translational neuroscience laboratory brought these structures back to the attention of the scientific community, renaming them CS-6 clusters (from chondroitin sulfate-6, which identifies their precise molecular composition) and demonstrating how

these structures were associated with glial cells and were severely reduced in the brains of people with psychotic disorders.

Then in 2017, Gabriele Chelini, newly hired in Berretta's lab, was tasked with revealing the function of these clusters.

"First we went to explore these structures in detail, visualizing them at very high resolution. We found that they are essentially clusters of synapses coated with CS-6 and organized in a clearly recognizable geometric shape. We then highlighted a new type of synaptic organization," the scholars recount.

"At this point, we had to use some 'experimental creativity'; with a combination of behavioral, molecular and refined morphological approaches, we realized that these connections encapsulated in CS-6 clusters change in response to electrical activity in the brain."

"Finally, through collaboration with Alexander Dityatev at DZNE Magdeburg, and the efforts of Hadi Mirzapourdelavar from his group, we attenuated the expression of CS-6 in the hippocampus (the region of the brain responsible for spatial learning), and demonstrated that the presence of CS-6 is necessary for synaptic plasticity and spatial memory," Bozzi and Chelini point out.

"This work paves the way for a new way of thinking about brain functioning. It is possible that all synapses formed on different neurons within CS-6 clusters have the ability to respond chorally to specific environmental stimuli, and are involved in a common function aimed at learning and memory processes," they note.

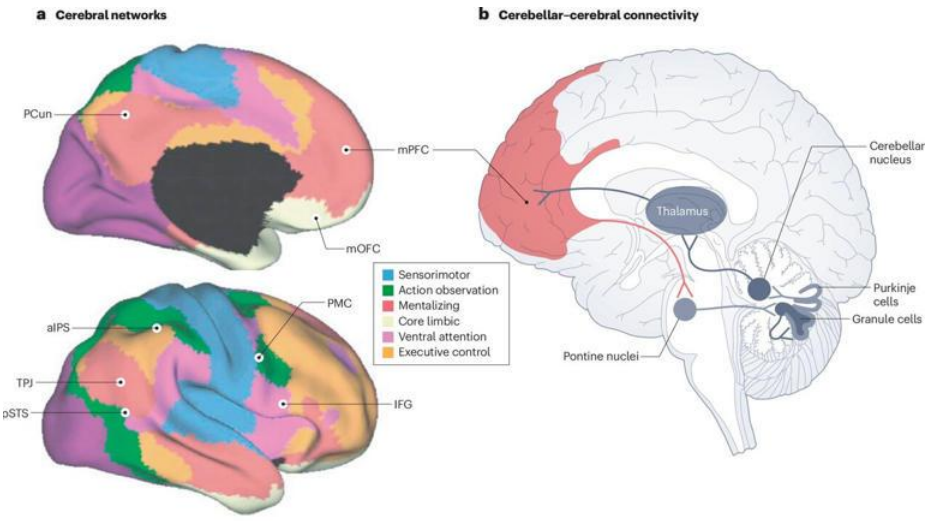
"They seem to represent a new substrate of information integration and association formation at the multicellular level," add Dityatev and Berretta.

The work is the result of a collaboration between several laboratories, including the translational neuroscience laboratory (Sabina Berretta; McLean Hospital—Harvard Medical School, Boston), the neurodevelopmental disorders research laboratory (Yuri Bozzi; CIMeC—Centro Interdipartimentale Mente/Cervello, University of Trento) and the Molecular Neuroplasticity laboratory (Alexander Dityatev; DZNE Magdeburg).

More information: Gabriele Chelini et al, Focal clusters of peri-synaptic matrix contribute to activity-dependent plasticity and memory in mice, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.114112

Provided by University of Trento

Research highlights crucial role of cerebellum in social and cognitive functioning



Cerebral networks and reciprocal connectivity between the cerebellum and cerebrum, supporting social and emotional learning. Credit: Nature Reviews Neuroscience (2024). DOI: 10.1038/s41583-024-00871-5

In a recent publication in *Nature Reviews Neuroscience*, Professor Frank Van Overwalle, from the Brain, Body and Cognition research group at the Vrije Universiteit Brussel (VUB), sheds light on the often-overlooked role of the cerebellum in both motor and social-cognitive processes. His research contributes to a growing shift in the field of neuroscience, which has traditionally focused on the cerebrum.

For decades, the cerebellum was primarily associated with motor coordination. "People with cerebellar abnormalities often experience motor issues," Van

Overwalle explains. "For example, they struggle to smoothly touch their nose with a finger. These difficulties highlight the cerebellum's essential role in refining motor movements."

Post doc researchers Naem Haihambo en Meijia Li perform cognition experiments to measure activity in the cerebellum. Credit: Frank Van Overwalle

However, Van Overwalle's research extends beyond motor functions, exploring the cerebellum's involvement in social and cognitive abilities. His findings reveal that abnormalities in the cerebellum not only lead to motor deficits but are also linked to emotional and behavioral disorders. He references research on individuals with autism, demonstrating how non-invasive brain stimulation techniques like magnetic stimulation can improve social task performance.

fMRI is a traditional technique for studying the (small) brain, but nowadays there are more affordable techniques, such as transcranial electrical stimulation. Credit: Frank Van Overwalle

"We've seen improvements in the sequence of cognitive tasks in people with autism through magnetic stimulation," says Van Overwalle. "We're now testing more complex tasks to see if these effects can be further enhanced, with the ultimate goal of developing practical treatments for people with autism."

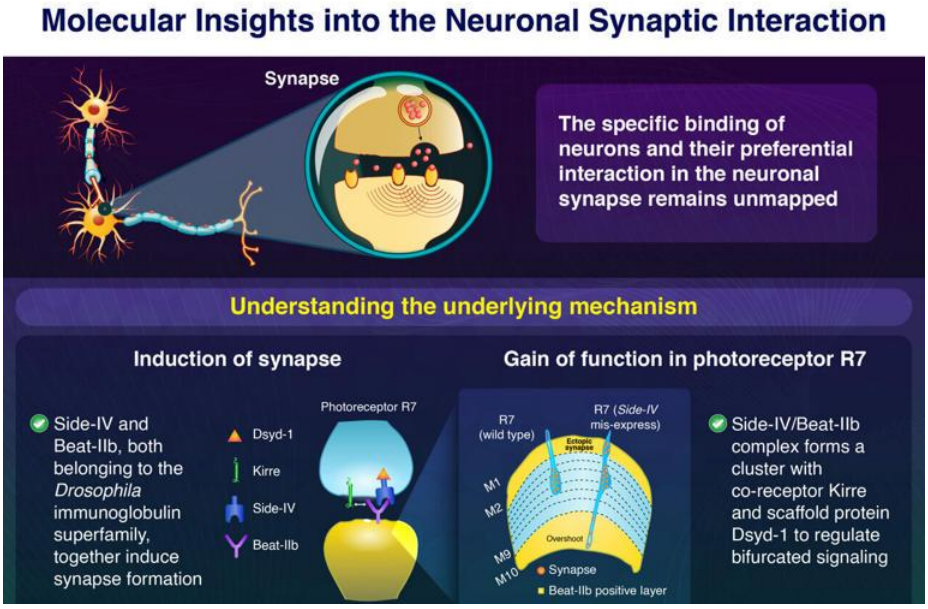
A notable breakthrough is the use of transcranial electrical stimulation (tES), a more affordable and accessible technique compared to magnetic stimulation. While the effects of tES are still limited, the research group is committed to further development, seeing its potential for wide-scale application in the future.

This research offers a fresh perspective on the cerebellum's role and paves the way for new treatments for psychiatric and neurological conditions, such as autism spectrum disorders. "Our hope is to refine these techniques further to improve social and cognitive functions in people with autism," concludes Van Overwalle.

More information: Frank Van Overwalle, Social and emotional learning in the cerebellum, *Nature Reviews Neuroscience* (2024). DOI: 10.1038/s41583-024-00871-5

Provided by Free University of Brussels

A molecular route to decoding synaptic specificity and nerve cell communication



This study provides insights into the molecular mechanisms underlying the neuronal synaptic interaction. Credit: Tokyo Tech© Provided by Medical Xpress

Neurons or nerve cells are the fundamental components of the central nervous system and are critically involved in signal transduction pathways. Transmission of information or signal from one neuron to another requires the establishment of a neuronal synapse: either chemical (neurotransmitters) or electrical (protein channels and ions). However, little is known about the underlying mechanism regarding the binding specificity and the ability to form preferential interactions between neuronal pairs.

In this regard, a team of researchers from Japan, led by Associate Professor Takashi Suzuki from the School of Life Science and Technology at Tokyo Institute of Technology (Tokyo Tech), recently attempted to unravel the molecular mechanisms behind the complex neuronal communication circuit.

Dr. Suzuki explains, "Take, for example, a person driving an automobile. The precise and rapid communication between the driver's perception and the

locomotor system can be the difference between life and death. The appropriate functioning of the nervous system ultimately comes down to a precise synaptic interaction between different types of neurons.

"Hence, our group focused on studying the molecular mechanisms of synaptic specificity using Drosophila, which allowed a genotypic as well as phenotypic assessment."

The researchers employed a combination of genomic and interactome (protein–protein interactions) analyses to identify the molecular mechanisms involved in synaptic communication.

The results revealed that the specific interaction of Side-IV/Beat-IIb immunoglobulin superfamily protein molecules was responsible for inducing the formation of synapse. This combination of Side-IV/Beat-IIb was central to the synaptic specificity between neurons. Side-IV/Beat-IIb, along with Side-IV's co-receptor, Kirre, and Dsyd-1, a synaptic scaffold protein, formed a cluster to regulate a preferential signaling mechanism among neuron pairs.

The research findings were published in *Cell Reports*.

Knockdown studies of synaptic scaffold protein Dsyd-1 and Liprin-α revealed the suppression of synapse formation. Moreover, Side-IV protein interaction with Dsyd-1 led to the formation of an active zone and resulted in a higher preference for synapse formation between specific neurons, thereby preventing miswiring.

Dr. Suzuki says, "We believe that our study can contribute to our current understanding of neuronal synapse and hierarchical ranking interactions among neuronal pairs. Future research involving higher order mutant species can build on our study to address the neurodegenerative disease landscape and aid in developing therapeutic strategies in the long term."

Overall, this study sheds valuable light on the molecular intricacies of neuronal communication.

More information: Jiro Osaka et al, Complex formation of immunoglobulin superfamily molecules Side-IV and Beat-IIb regulates synaptic specificity, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.113798

Provided by Tokyo Institute of Technology

Study reveals function of little-understood synapse in the brain

New research from Oregon Health & Science University for the first time reveals the function of a little-understood junction between cells in the brain that could have important treatment implications for conditions ranging from multiple sclerosis to Alzheimer's disease, to a type of brain cancer known as glioma.

The study is published in *Nature Neuroscience*.

Neuroscientists focused on the junction, or synapse, connecting neurons to a non-neuronal cell, known as oligodendrocyte precursor cells, or OPCs. OPCs can differentiate into oligodendrocytes, which produce a sheath around nerves known as myelin. Myelin is the protective sheath covering each nerve cell's axon—the threadlike portion of a cell that transmits electrical signals between cells.

The study found that these synapses play a pivotal role in producing that myelin.

"This is the first investigation of these synapses in live tissue," said senior author Kelly Monk, Ph.D., professor and co-director of the Vollum Institute at OHSU. "This gives an understanding of the basic, fundamental properties of how these cells work in normal development. In the future, we might look at how they function differently in the context of MS patients."

The fact that these synapses exist at all was the subject of a landmark discovery by OHSU researchers at the Vollum that was published in the journal *Nature* in May 2000. Until that point, synapses in the brain had been known only to carry neurotransmitters between neurons, so the discovery of a synapse between neurons and OPCs came as a revelation.

"After two decades, we still didn't know what these synapses do," Monk said.

Scientists tackled the problem by using single-cell imaging of live tissue in zebrafish, whose transparent bodies enable researchers to see the inner workings of their central nervous system in real time. Using powerful new tools in imaging,

pharmacology and gene editing, researchers were able to use neuron-OPC synapses to predict the timing and location of the formation of myelin.

The findings are likely the tip of the iceberg in terms of understanding the importance of these synapses, said lead author Jiaxing Li, Ph.D., a postdoctoral fellow in Monk's lab.

Oligodendrocyte precursor cells comprise about 5% of all cells in the brain—meaning the synapses they form with neurons could be relevant to many disease conditions, including the formation of cancerous tumors.

Li noted that previous studies have suggested a role for OPCs in a range of neurodegenerative conditions, including demyelinating disorders such as MS, neurodegenerative diseases such as Alzheimer's and even psychiatric disorders like schizophrenia.

By demonstrating the basic function of the synapse between neurons and OPCs, Li said the study may lead to new methods of regulating OPC function to alter disease progression. For example, these synapses could be the key to promoting remyelination in conditions such MS, where myelin has been degraded. In MS, this degradation can slow or block electric signals required for people to see, move their muscles, feel sensations and think.

"There may be a way to intervene so that you can increase the myelin sheath," he said.

Monk said the discovery may be most immediately relevant to cancer.

"In glioma, these synapses are hijacked to drive tumor progression," she said. "It may be possible to modulate the synaptic input involved in tumor formation, while still allowing for normal synaptic signaling."

Even though these precursor cells comprise roughly 5% of all human brain cells, only a fraction go on to form oligodendrocytes.

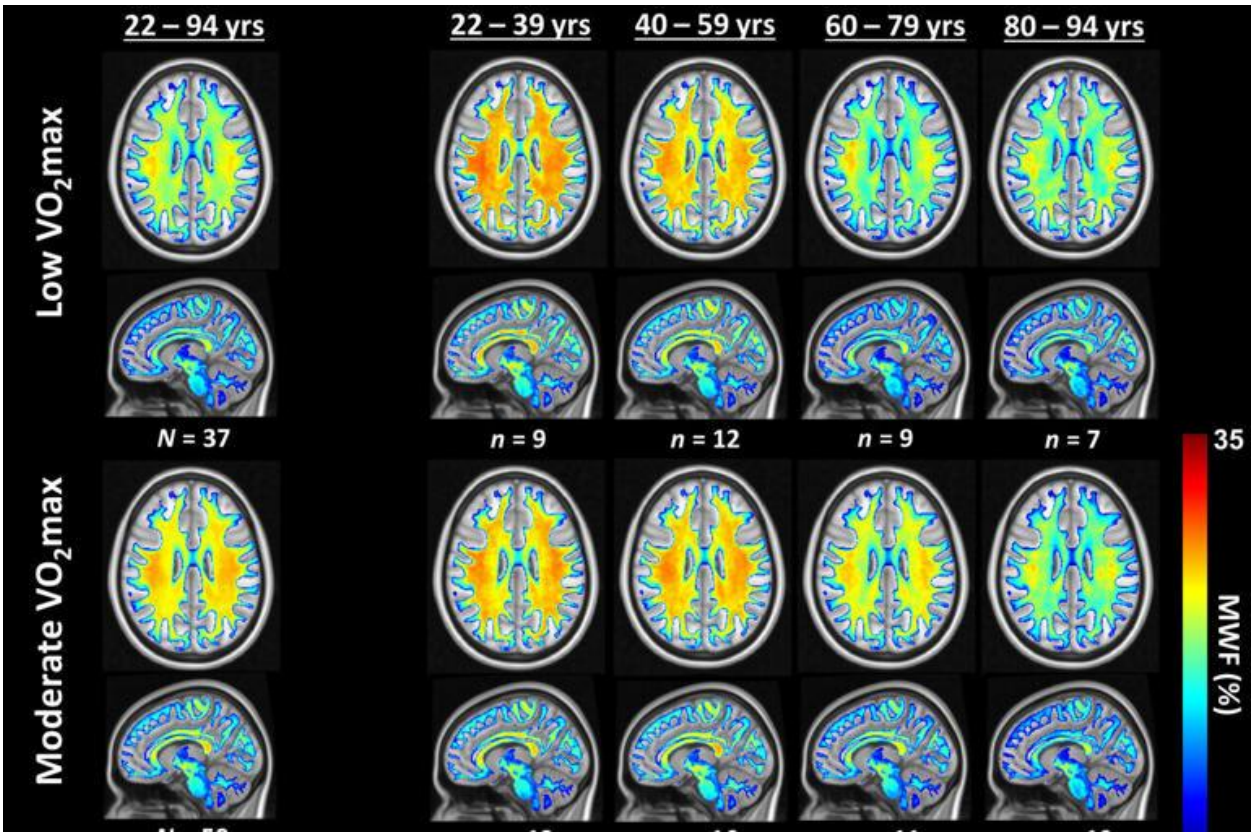
"It's becoming pretty clear that these OPCs have other functions aside from forming oligodendrocytes," Monk said. "From an evolutionary perspective, it doesn't make sense to have so many of these precursor cells in your brain if they're not doing something."

Their synaptic connection to neurons therefore likely plays a fundamental role in the brain, and is worthy of future exploration, she said.

In addition to Monk and Li, co-authors include Tania Miramontes of OHSU and Tim Czopka, Ph.D., of the Centre for Clinical Brain Sciences at the University of Edinburgh in the U.K.

More information: Synaptic input and Ca2+ activity in zebrafish oligodendrocyte precursor cells contribute to myelin sheath formation, *Nature Neuroscience* (2024). DOI: 10.1038/s41593-023-01553-8. www.nature.com/articles/s41593-023-01553-8

Brain training: Study links cardiovascular fitness to brain health



Examples of axial and sagittal MWF parameter maps averaged across participants with either lower, moderate, or higher VO2max levels. Participants were drawn from the full age range as well as from restricted age ranges to mitigate the effect of age. Results are shown for representative slices. Visual inspection indicates that, overall, participants with higher VO2max levels exhibit greater regional MWF values, especially at middle and older ages. Credit: Proceedings of the National Academy of Sciences (2024). DOI: 10.1073/pnas.2402813121

The brain's white matter comprises areas of the central nervous system made up of myelinated axons. Its name is derived from the pale appearance of the lipids that comprise myelin. Myelin is a segmented sheath that insulates axons, ensuring the conduction of neural signals. The loss of myelin is documented in a number of neurodegenerative pathologies, including Alzheimer's and Parkinson's disease, and perhaps most notably, multiple sclerosis. As people age, demyelination becomes more likely.

Researchers have long suspected a relationship between cardiorespiratory fitness and the integrity of the brain's white matter as people age. However, a lack of specific evidence has led researchers at the National Institutes of Health to conduct a study examining the strength of this correlation, now published in the *Proceedings of the National Academy of Sciences*.

To establish a correlation between cardiovascular fitness and cerebral myelination, the researchers recruited a cohort of 125 participants from age 22 to 94 years old. The cardiovascular fitness of the participants was quantified as the maximum rate of oxygen consumption, popularly and succinctly known as VO_2max. Myelin content was defined as the myelin water fraction, which the researchers estimated through an advanced multicomponent relaxometry MRI method.

Previous investigations relying on conventional techniques were not able to isolate myelin from other brain matter; the new MRI technique employed here is more sensitive and specific to measuring myelin content in vivo. In fact, recent studies using multicomponent relaxometry MRI established correlations between local myelin water fraction with cerebral blood flow and motor function, both of which are influenced by cardiorespiratory fitness, which in turn motivated the NIH researchers to pursue the current study using the same technology.

Results

The researchers report that higher cardiorespiratory fitness correlated strongly with greater cerebral myelination. Further, higher cardiorespiratory fitness was associated with better myelin integrity, which was particularly notable in the middle-aged and older participants.

Notably, they found significant positive correlations between the two measures in the frontal lobes and white matter tracts—regions susceptible to early degeneration associated with neurological disorders at the onset of old age. They suggest that cardiorespiratory fitness is likely to be significantly protective for these sensitive brain regions, particularly among the subjects with lifelong fitness.

The researchers note that they were unable to establish a causal link between improved cardiorespiratory fitness and improved myelin integrity and that their results represent a correlation only.

"Nevertheless, our findings suggest that cardiorespiratory fitness is likely to be a valuable indicator of overall health and a potential target for interventions aimed at promoting brain health," they write.

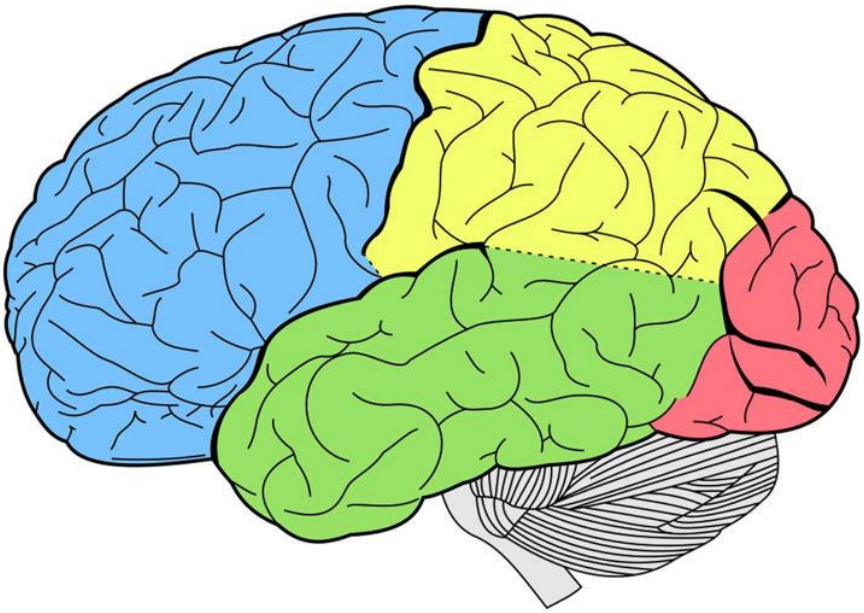
The study also notes the association of aerobic exercise with neuroprotective adaptations in the brain, as well as the upregulation of neurotrophins and brain-derived neurotrophic factor, which increases brain mitochondrial function. Declines in mitochondrial function have been previously associated with diseases resulting from demyelination.

The researchers suggest that future studies could use their work to study the relationship between physical fitness, brain health and myelin integrity to support brain aging and prevent neurological disorders.

They write, "Additionally, this work lays the foundation for further investigations into the potential therapeutic applications of improving cardiorespiratory fitness or myelination to promote healthy brain aging and combat age-related neurodegeneration, including in Alzheimer's disease."

More information: Evidence of association between higher cardiorespiratory fitness and higher cerebral myelination in aging. *Proceedings of the National Academy of Sciences*. DOI: 10.1073/pnas.2402813121

The middle-aged brain changes a lot—and it's key to understanding dementia



Our brains change more rapidly at various times of our lives, as though life's clock was ticking faster than usual. Childhood, adolescence and very old age are good examples of this. Yet for much of adulthood, the same clock seems to tick fairly regularly. One lap around the sun; one year older.

However, there may be a stage of life when the brain's clock starts speeding up. The brain starts changing without you necessarily noticing it. It may even be caused (partly) by what's in your blood. This stage of brain aging during your 40s to 50s, or "middle-aging", may predict your future health.

Psychologists studying how our mental faculties change with age find that they decline gradually, starting in our 20s and 30s. However, when assessing people's memory of everyday events, the change over time appears to be especially rapid and unstable during middle age. That is, even among healthy people, some experience rapidly deteriorating memory, while for others, it may even improve.

This suggests that the brain may be going through accelerating, as opposed to gradual, change during this period. Several structures of the brain have been found to change in midlife. The hippocampus, an area critical for forming new memories, is one of them.

It shrinks throughout much of adulthood, and this shrinkage seems to accelerate around the time of middle age. Abrupt shifts in the size and function of the hippocampus during middle age could underlie memory changes like the ones mentioned above.

Ultimately, what allows the brain to carry out its functions are the connections between brain cells—the white matter. These connections mature slowly throughout adulthood, especially the ones connecting areas of the brain that deal with cognitive functions such as memory, reasoning and language.

Interestingly, during middle age, many of them go through a turning point, from gaining volume to losing volume. This means that signals and information cannot be transmitted as fast. Reaction time starts deteriorating around the same time.

Through the white matter connections, brain areas talk to each other and form interconnected networks that can perform cognitive and sensory functions, including memory or vision. While the sensory networks deteriorate gradually throughout adulthood, the cognitive networks start deteriorating faster during middle age, especially those involved in memory.

Much like how highly connected people in society tend to form cliques with each other, brain regions do the same through their connections. This organization of the brain's communication allows us to perform some of the complex tasks we might take for granted, such as planning our days and making decisions.

The brain seems to peak in this regard by the time we hit middle age. Some have even referred to middle age as a "sweet spot" for some types of decision-making, but then the network "cliques" start to break up.

It's worth stating at this point why these subtle changes matter. The global population aged 60 and over is set to roughly double by 2050, and with this, unfortunately, will come a considerable increase in dementia case numbers.

Focus has been too much on the brain in old age

Science has long focused on very old age, when the detrimental effects of time are most obvious, but, by then, it can often be too late to intervene. Middle age could be a period when we can detect early risk factors of future cognitive decline, such as in dementia. Critically, the window of opportunity to intervene may also still be open.

So, how do we detect changes without having to give everyone an expensive brain scan? As it turns out, the contents of blood may cause the brain to age. With time, our cells and organs slowly deteriorate, and the immune system can react to this by starting the process of inflammation. Inflammatory molecules can then end up in the bloodstream, make their way to the brain, interfere with its normal functioning and possibly impair cognition.

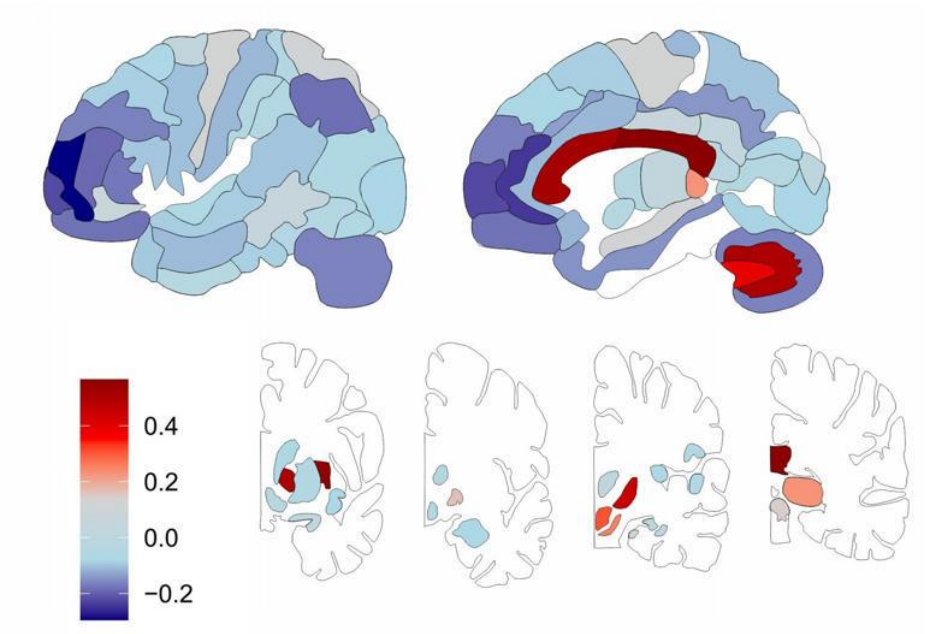
In a fascinating study, scientists from Johns Hopkins and the University of Mississippi analyzed the presence of inflammatory molecules in the blood of middle-aged adults and were able to predict future cognitive change 20 years down the line. This highlights an important emerging idea: age in terms of biological measures is more informative about your future health than age in terms of years lived.

Importantly, biological age can often be estimated with readily available and cost-effective tests used in the clinic.

"Middle aging" may be more consequential for our future brain health than we think. The hurried ticking of the clock could be slowed from outside the brain. For example, physical exercise confers some of its beneficial effects on the brain

through blood-borne messengers. These can work to oppose the effects of time. If they could be harnessed, they might steady the pendulum.

Scientists map the distribution of lipids in the human brain



Distribution of cholesterol in the human brain. Credit: Maria Osetrova© Provided by Medical Xpress

Scientists have found that 93% of the lipids in brain tissue are distributed differently in the white and gray matter, the subcortex, the visual and motor cortices, and the prefrontal cortex, which is responsible for decision-making, social behavior, and other functions.

Abnormalities in the brain lipidome tend to occur in mental and cognitive disorders, so mapping these molecules should help gain more information about the disease. The research was published in *Nature Communications*.

A major component of brain tissue, lipids are fatty compounds that make up 35%–40% of all the molecules in the gray matter cell bodies and as much as 78%

of the axons' myelin sheaths in the white matter. Brain tissue lipids are very diverse and include cholesterol, phosphorus-containing compounds, such as phospholipids and sphingolipids, and other molecules.

Since lipids are involved in the metabolism and growth of neurons, the delivery of signals between cells and the control of inflammatory processes, abnormalities in the lipidome composition have been associated with cognitive disorders, such as autism, schizophrenia, and Alzheimer's disease.

However, the relationship between the lipidome and the structural features of brain tissue remains poorly understood, limiting the use of lipids as molecular markers for detecting brain diseases.

Researchers from the Skolkovo Institute of Science and Technology and their colleagues have created the world's first map of human brain lipids. They studied brain tissue samples from four healthy individuals and assessed the lipid composition in 75 different parts of the brain.

The lipids in the samples were identified using mass spectrometry, which allows determining a molecule's structure from the mass to charge ratio and its motion pattern in a magnetic field.

The researchers found a total of 419 different lipids, most of them (93%) unevenly distributed among the different parts of the human brain. For example, the subcortex (the oldest part of the brain), motor and visual cortices had relatively high levels of cholesterol, while the prefrontal cortex responsible for complex social behavior and decision-making had relatively low levels of this lipid.

Since most lipids are found in the myelin sheaths, the team checked whether the myelin content in a particular part of the brain affected its typical lipidome. The myelin-rich white matter turned out to contain mostly ceramides, two classes of phospholipids, and lipids with saturated fatty acids.

Since the main function of the white matter is to transmit signals via axons, these types of lipids are thought to be essential for the tissue to perform its function.

Polyunsaturated fatty acid lipids prevailed in the gray matter, which contains a concentration of cell bodies rather than axons and virtually no myelin. This suggests that such molecules may be important for signal processing in cells.

"In the future, we plan to thoroughly investigate the subcortical lipidome which was only partially covered by this research, and to study brain samples from patients with various mental disorders.

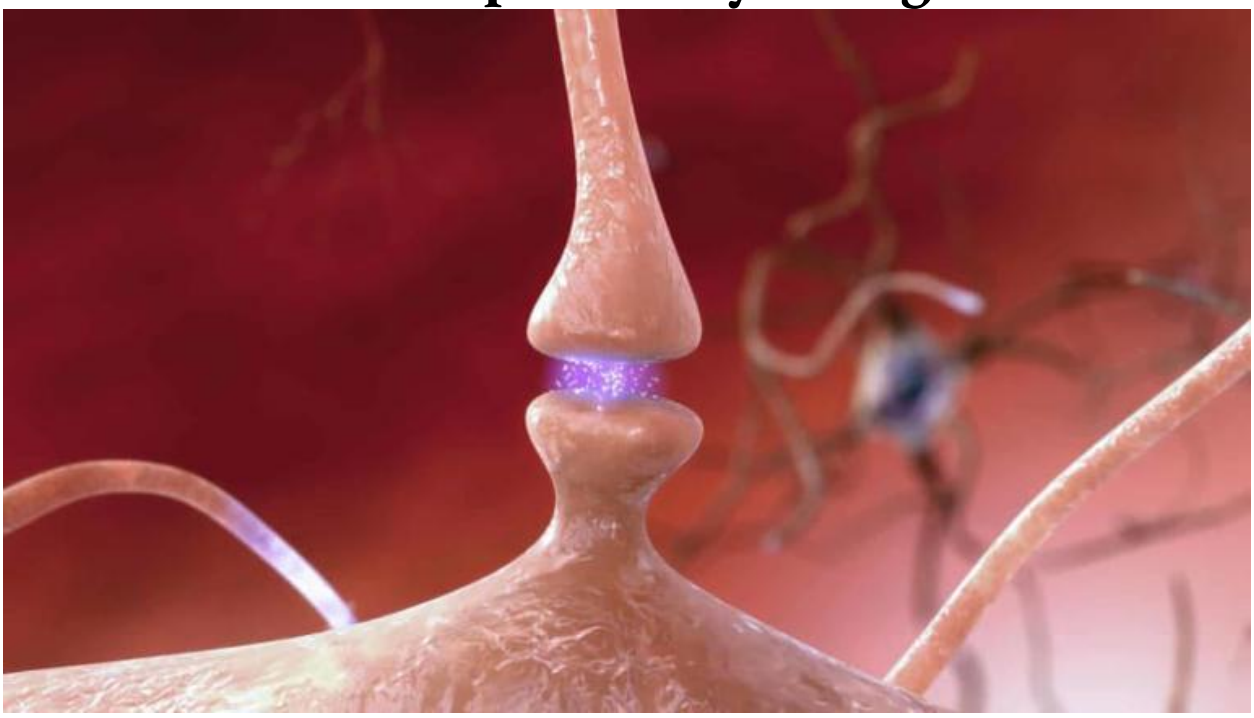
"The potential complete 'decoding' of the lipidome will help us to better understand the nature of mental illness and its impact on the structure and functioning of the brain," said Maria Osetrova, a research engineer at the Skoltech Neuro Center.

Other organizations involved in this research included Lomonosov Moscow State University, the Semenov Federal Research Center for Chemical Physics of RAS (Moscow), the University of Leipzig (Germany), and the National University of Singapore.

More information: Maria Osetrova et al, Lipidome atlas of the adult human brain, *Nature Communications* (2024). DOI: 10.1038/s41467-024-48734-y

Provided by Skolkovo Institute of Science and Technology

Human brain can store 10 times more information than previously thought



Our memories and thoughts stem from complex patterns of electrical and chemical activity in the brain. Central to this activity are synapses, the junctions where branches of neurons connect, similar to electrical wires. Here, an axon from one neuron links to a dendrite of another. At these synapses, neurotransmitters carry signals across the gap, instructing the receiving neuron to pass on an electrical signal to others. Remarkably, each neuron can form thousands of these connections.

Similar to computers, we measure the brain's memory storage in "bits," and the number of bits it can hold rests on the number and strength of its synapses. It's worth noting that brains are analog — just so you don't get the wrong idea. Brains process everything in parallel, in continuous time rather than in discrete intervals, so the "bit" (the smallest unit of digital data) in this case is not a perfect analogy for how information is stored in a biological system. Nevertheless, it serves the purpose of estimating information processing.

Previously, it was believed that synapses came in very limited sizes and strengths. However, recent research suggests otherwise. The human brain's capacity to store information is almost ten times greater than previously estimated, according to a new study.

New Insights into Synaptic Strength and Memory Storage

A team of researchers from the University of California, San Diego and the Salk Institute developed a highly precise method to assess the strength of synapses in the brain of a rat. These synapses, where brain cells communicate and store information, play a critical role in learning and memory. By understanding how synapses strengthen and weaken, the scientists precisely quantified the information storage capacity of these connections.

In the human brain, over 100 trillion synapses exist between neurons. These synapses facilitate information transfer across the brain by launching chemical

messengers. As we learn, specific synapses strengthen, enabling us to retain new information. This process is known as synaptic plasticity, is essential for memory formation and cognitive function.

When neurons talk, they do so at different volumes — some neurons whisper to each other while others shout. The 'volume' setting of the synapse, or the synaptic strength, is not static, but rather can change in both the short term and long term. Synaptic plasticity refers to these changes in synaptic strength.

However, aging and neurological diseases like Alzheimer's can weaken synapses, reducing our cognitive ability. This is why studies like these are important — they can help scientists unlock new therapies that may stave off or even cure neurodegenerative diseases that currently plague millions of patients across the world. However, measuring the strength of synapses has traditionally been challenging.

The team analyzed pairs of synapses from a rat hippocampus, a brain region vital for learning and memory. The new study's method leverages information theory, which allows scientists to quantify how much information synapses can store and transmit. What this means is that a framework typically reserved for computers was applied to the brain in order to estimate the number of bits that synapses can hold. They found that these pairs of synapses responded to the same type and amount of brain signals, performing synaptic strength adjustment.

Current and Future Potential

Ultimately, this analysis indicated that hippocampal synapses could store between 4.1 and 4.6 bits of information. Scientists thought each synapse could hold one bit. Overall, this means the human brain could store ten times more information than previously thought, or at least a petabyte — that's as much as 500 billion DVDs or all the movies ever made in high-definition.

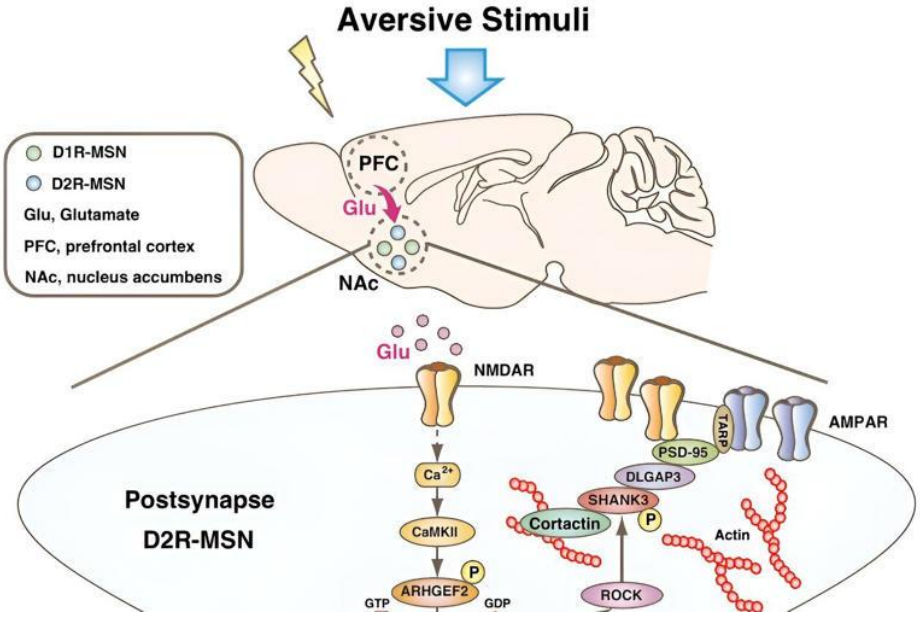
While the study focuses on a small part of the rat brain, future research could explore how information storage capacity varies across different brain areas and species. This method could also compare healthy and diseased brain states, offering insights into conditions that affect cognitive functions.

In 2016, the Salk researchers reached the same conclusions. The new findings serve to confirm this initial assessment. Back then, the researchers also made another important revelation: there are at least 26 size categories of synapses, rather than just a few.

These findings also provide insight into the brain's remarkable efficiency. Despite its complexity, the waking adult brain uses only about 20 watts of continuous power, comparable to a very dim light bulb. These discoveries could inspire computer scientists to design highly precise yet energy-efficient computers. These innovations could particularly benefit "deep learning" and artificial neural networks, enhancing their capabilities in areas like speech recognition, object identification, and language translation.

The findings appeared in the journal *Neural Computation*.

Gaining insights into the chemical basis of aversive learning



This study focused on how NMDAR, an important cell surface receptor, triggers a complex chemical cascade in postsynaptic neurons in the nucleus accumbens region of the brain. More specifically, the researchers used an innovative methodology to investigate phosphorylation events downstream of NMDAR activation, shedding light on

the intricacies of the chemistry related to aversive learning in mice. Credit: Science Signaling (2024). DOI: 10.1126/scisignal.ado9852

One of the things that makes brains so incredibly difficult to understand is their ability to adjust and adapt. Our learning experiences can set off complex signaling cascades that reshape neurons—and their synaptic connections—at the cellular level.

For example, in mammals, scientists have established that activation of the N-methyl-D-aspartate receptor (NMDAR) and the ensuing calcium ion (Ca^{2+})-dependent signaling cascade is essential for postsynaptic remodeling and learning. As one might reasonably expect, problems with NMDAR have been linked to neuropsychiatric disorders, including epilepsy, schizophrenia, autism, and intellectual disabilities.

Understanding the functions of NMDAR is therefore key to understanding many neuropathologies and developing treatments. Unfortunately, research in this field has been challenging because of the complexity of how NMDAR causes some of its downstream effects. More specifically, NMDAR activation triggers Ca^{2+}-dependent kinases, such as CaMKII, that phosphorylate other target proteins.

Phosphorylation is a chemical process that modifies proteins, acting as a molecular switch to turn various cellular functions on or off. Although these modifications are central to the functions of NMDAR, studying phosphorylation events and their roles in signaling pathways has proven difficult.

At Fujita Health University in Japan, a research team led by Professor Kozo Kaibuchi has been pioneering a novel screening method to study phosphoproteomics—the comprehensive analysis of phosphorylated proteins. In a paper published in *Science Signaling* on 10 September 2024, they employed this technique to shed light on how intracellular NMDAR signaling regulates synaptic plasticity and learning through phosphorylation events.

Other members of the team included Senior Assistant Professor Yasuhiro Funahashi, Dr. Rijwan Uddin Ahammad, Professor Taku Nagai and Professor Takayuki Yamashita from Fujita Health University, Professor Yukihiko Noda from

Meijyo University, Professor Kiyofumi Yamada from Nagoya University and Professor Shigeo Uchino from Teikyo University.

The above-mentioned method is called kinase-oriented substrate screening (KIOSS), which uses affinity beads coated with domains that bind to phosphorylated serine and threonine residues. Using KIOSS, the researchers investigated phosphorylation events downstream of NMDAR in isolated mice brain slices of the nucleus accumbens (NAc), a key brain structure that is involved in emotional responses, motivation, and various forms of learning. Using an NMDAR agonist to induce a higher Ca^{2+} influx in neurons, they screened proteins phosphorylated by CaMKII.

The researchers found 194 proteins that fit this criterion, but they focused specifically on Rho GTPase regulators, which are known to play a crucial role for synaptic remodeling in learning. Interestingly, they observed that phosphorylation of a specific regulator called ARHGEF2 led to the activation of RhoA, which in turn activated Rho-kinase/ROCK, a protein necessary for proper neuronal development and structure.

The team decided to delve deeper into the effects of ROCK activation in this context, as Prof. Kaibuchi explains, "ROCK inhibition impairs memory formation, including long-term spatial memory in the hippocampus and fear conditioning memory in the lateral amygdala. However, it remains unclear whether ROCK regulates aversive learning in the NAc. Thus, we used mice in a passive avoidance test, a fear-motivated test classically used to assess memory in laboratory animals, to examine whether ROCK regulates aversive learning."

The researchers ultimately identified 221 candidate substrates of ROCK, and demonstrated via in vivo experiments that aversive stimuli activated the CaMKII–RhoA–ROCK pathway. Inhibiting this pathway chemically or through genetic modifications resulted in impaired aversive learning, cementing the results.

Worth noting, the researchers put all the data derived from this study in a publicly available database they had previously developed. "The phosphorylated proteins and their phosphorylation sites identified in this work are registered in our KANPHOS database," said Prof. Kaibuchi,.

"KANPHOS provides extensive data on different aspects of phosphorylation in the brain, including extracellular and intracellular signaling pathways, phosphorylated

proteins, phosphorylation sites, responsible kinases, mouse models, and related behaviors and diseases. These data and the KANPHOS database itself form a useful resource for elucidating the mechanisms of NMDAR signaling in the brain."

Taken together, the contributions of this study could be foundational to achieving a better understanding of many neuronal diseases. "The signaling pathways downstream of NMDAR involved in aversive learning we identified may provide insights into the mechanisms underlying the pathophysiology of psychiatric disorders such as schizophrenia," concludes Prof. Kaibuchi.

"The next step is to explore how these findings can contribute to the development of treatments aimed at ameliorating symptoms of these disorders," he adds.

More information: Yasuhiro Funahashi et al, Signal flow in the NMDA receptor–dependent phosphoproteome regulates postsynaptic plasticity for aversive learning, *Science Signaling* (2024). DOI: 10.1126/scisignal.ado9852

Provided by Fujita Health University

Study of 3.4 million individual cells suggests Alzheimer's damages brain in two distinct phases

Alzheimer's disease may harm the brain in two distinct phases, according to a new study funded by the National Institutes of Health and published in *Nature Neuroscience*. Using advanced brain mapping techniques, researchers discovered that in the first phase, which occurs before any symptoms appear, certain types of brain cells are gradually damaged. In the second phase, the disease accelerates, causing widespread brain damage that coincides with memory loss and other noticeable symptoms. These findings could change the way scientists understand Alzheimer's and open up new possibilities for developing targeted treatments.

The motivation behind this research stems from the difficulty in diagnosing Alzheimer's early, as much of the brain damage occurs before symptoms become

apparent. Alzheimer's disease is characterized by a gradual loss of brain function due to the buildup of plaques and tangles—protein clumps that interfere with communication between brain cells. Researchers wanted to understand these early, silent changes in the brain in greater detail. By identifying the first signs of damage at the cellular level, they hoped to create opportunities for early intervention, potentially halting or slowing the progression of the disease before significant memory loss and cognitive decline occur.

"One of the challenges to diagnosing and treating Alzheimer's is that much of the damage to the brain happens well before symptoms occur. The ability to detect these early changes means that, for the first time, we can see what is happening to a person's brain during the earliest periods of the disease," said Richard J. Hodes, the director of the NIH National Institute on Aging. "The results fundamentally alter scientists' understanding of how Alzheimer's harms the brain and will guide the development of new treatments for this devastating disorder."

To carry out the study, scientists analyzed brain tissue from 84 donors who had died at various stages of Alzheimer's disease. These tissue samples were obtained from long-term studies, such as the Adult Changes in Thought study and the University of Washington Alzheimer's Disease Research Center.

The focus was on a brain region called the middle temporal gyrus, which is critical for memory, language, and vision and is especially vulnerable to Alzheimer's-related damage. Using advanced genetic analysis and brain mapping tools developed as part of the NIH's Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, the researchers studied over 3.4 million individual brain cells. This allowed the research team to create a detailed timeline of cellular changes in the brain.

The researchers discovered that Alzheimer's impacts the brain in two distinct phases. In the first phase, which can begin years before any symptoms show, certain brain cells, particularly inhibitory neurons, start to die. Inhibitory neurons play a key role in regulating brain activity, and their loss may disrupt neural circuits, potentially setting the stage for further brain damage. Interestingly, these cells, known as somatostatin inhibitory neurons, were found to be among the first to be affected in the early stages of the disease. This was a surprising finding, as previous studies suggested that Alzheimer's primarily damages excitatory neurons, which are responsible for stimulating brain activity.

In contrast, the second phase of Alzheimer's, which aligns with the appearance of symptoms like memory loss, involves a rapid spread of damage. This phase is characterized by widespread inflammation, increased cell death, and the accumulation of plaques and tangles in the brain. By the time symptoms become noticeable, the brain is already experiencing significant structural damage. The researchers emphasized that this second phase is when most of the traditionally studied Alzheimer's markers, such as plaques and tangles, appear rapidly.

One of the most important findings of the study was that the early phase of Alzheimer's is relatively "quiet," meaning that the damage happens gradually and without noticeable symptoms. During this period, plaques begin to form slowly, and the brain's immune system becomes activated, but the damage to the brain's structure is minimal. The insulation around neurons, which helps transmit signals efficiently, also starts to degrade. However, it is the death of the inhibitory neurons that appears to trigger the more extensive changes that come later.

This discovery challenges the traditional view that excitatory neurons are the primary victims of Alzheimer's disease. The researchers proposed that the loss of inhibitory neurons may lead to an imbalance in brain signaling, which could contribute to the breakdown of neural circuits and the eventual onset of symptoms. Additionally, the study confirmed previous findings about how Alzheimer's affects the brain, while also identifying new cellular changes that occur during the disease's progression.

Further supporting this idea, a separate NIH-funded study at the Massachusetts Institute of Technology found that certain genes, including one called REELIN, may influence how vulnerable neurons are to Alzheimer's. This gene, along with the involvement of star-shaped brain cells known as astrocytes, could provide new insights into why some brain cells are more resistant to damage. These findings align with the current research, which also pointed to astrocytes as potentially playing a protective role in the brain.

While this study represents a significant step forward in understanding the early stages of Alzheimer's, there are some limitations. The research focused primarily on a single brain region, the middle temporal gyrus, which is known to be heavily affected by Alzheimer's. However, Alzheimer's impacts multiple brain regions, so future research could expand this approach to other areas to build a more comprehensive map of the disease's progression across the entire brain.

Additionally, the study relied on postmortem brain samples, which provide a snapshot of the disease at various stages, but cannot capture the dynamic process of Alzheimer's development over time in a living brain.

Another limitation is the challenge of translating these findings into treatments. While the discovery of early cellular changes offers hope for new interventions, it remains difficult to detect Alzheimer's at these early stages in living patients. Developing tools to monitor these early changes in real time will be critical for creating treatments that can target the disease before symptoms appear.

In the future, researchers aim to build on this work by exploring how these early changes might be detected through brain scans or blood tests. They are also interested in studying how these cellular changes interact with genetic risk factors, such as the presence of the APOE4 gene, which is known to increase the likelihood of developing Alzheimer's. By understanding how genetic factors influence the brain's vulnerability to damage, scientists may be able to identify individuals who are at risk and intervene even earlier.

"This research demonstrates how powerful new technologies provided by the NIH's BRAIN Initiative are changing the way we understand diseases like Alzheimer's. With these tools, scientists were able to detect the earliest cellular changes to the brain to create a more complete picture of what happens over the entire course of the disease," said John Ngai,the director of The BRAIN Initiative®. "The new knowledge provided by this study may help scientists and drug developers around the world develop diagnostics and treatments targeted to specific stages of Alzheimer's and other dementias."

Upgrading brain storage: Quantifying how much information our synapses can hold

Two neurons, one in full (left, light purple) and one partially out of frame (right, light blue) on top of a background of zeros and ones to symbolize the unit of bits used to quantify information storage in synapses. The neuron on the left is sending messages to the neuron on the right. The electrical pulse of synapses processing and sending information is represented by flashes of yellow where the two neurons meet. Credit: Salk Institute© Provided by Medical Xpress

With each flip you make through a deck of vocabulary word flashcards, their definitions come more quickly, more easily. This process of learning and

remembering new information strengthens important connections in your brain. Recalling those new words and definitions more easily with practice is evidence that those neural connections, called synapses, can grow stronger or weaker over time—a feature known as synaptic plasticity.

Quantifying the dynamics of individual synapses can be a challenge for neuroscientists, but recent computational innovations from the Salk Institute may be changing that—and revealing new insights about the brain along the way.

To understand how the brain learns and retains information, scientists try to quantify how much stronger a synapse has gotten through learning, and how much stronger it can get. Synaptic strength can be measured by looking at the physical characteristics of synapses, but it's much more difficult to measure the precision of plasticity (whether synapses grow weaker or stronger by a consistent amount) and the amount of information a synapse can store.

White arrows pointing at two synapses (red) on the same dendrite (yellow), sharing the same axon (spotted black tube). Credit: Salk Institute© Provided by Medical Xpress

Salk scientists have established a new method to explore synaptic strength, precision of plasticity, and amount of information storage. Quantifying these three synaptic features can improve scientific understanding of how humans learn and remember, as well as how those processes evolve over time or deteriorate with age or disease. The findings were published in *Neural Computation* on April 23, 2024.

"We're getting better at identifying exactly where and how individual neurons are connected to each other, but we still have a lot to learn about the dynamics of those connections," says Professor Terrence Sejnowski, senior author of the study and holder of the Francis Crick Chair at Salk.

"We have now created a technique for studying the strength of synapses, the precision with which neurons modulate that strength, and the amount of information synapses are capable of storing—leading us to find that our brain can store 10 times more information than we previously thought."

When a message travels through the brain, it hops from neuron to neuron, flowing from the end of one neuron into the outstretched tendrils, called dendrites, of another. Each dendrite on a neuron is covered with tiny bulbous appendages, called dendritic spines, and at the end of each dendritic spine is the

synapse—a tiny space where the two cells meet, and an electrochemical signal is transmitted. Different synapses are activated to send different messages.

Some messages activate pairs of synapses, which live near one another on the same dendrite. These synapse pairs are a fantastic research tool—if two synapses have identical activation histories, scientists can compare the strength of those synapses to draw conclusions about the precision of plasticity.

Since the same type and amount of information has passed through these two synapses, did they each change in strength by the same amount? If so, their precision of plasticity is high.

The Salk team applied concepts from information theory to analyze synapse pairs from a rat hippocampus—a part of the brain involved in learning and memory—for strength, plasticity, and precision of plasticity.

Information theory is a sophisticated mathematical way of understanding information processing as an input traveling through a noisy channel and being reconstructed on the other end.

Crucially, unlike methods used in the past, information theory accounts for the noisiness of the brain's many signals and cells, in addition to offering a discrete unit of information—a bit—to measure the amount of information stored at a synapse.

"We divided up synapses by strength, of which there were 24 possible categories, then compared special synapse pairs to determine how precisely each synapses' strength is modulated," says Mohammad Samavat, first author of the study and a postdoctoral researcher in Sejnowski's lab.

"We were excited to find that the pairs had very similar dendritic spine sizes and synaptic strengths, meaning the brain is highly precise when it makes synapses weaker or stronger over time."

In addition to noting the similarities in synapse strength within these pairs, which translates to a high level of precision of plasticity, the team also measured the amount of information held in each of the 24 strength categories. Despite differences in the size of each dendritic spine, each of the 24 synaptic strength categories held a similar amount (between 4.1 and 4.6 bits) of information.

Compared to older techniques, this new approach using information theory is (1) more thorough, accounting for 10 times more information storage in the brain than was previously assumed, and (2) scalable, meaning it can be applied to diverse and large datasets to gather information about other synapses.

"This technique is going to be a tremendous help for neuroscientists," says Kristen Harris, a professor at the University of Texas at Austin and an author of the study. "Having this detailed look into synaptic strength and plasticity could really propel research on learning and memory, and we can use it to explore these processes in all different parts of human brains, animal brains, young brains, and old brains."

Sejnowski says future work by projects like the National Institutes of Health's BRAIN Initiative, which established a human brain cell atlas in October 2023, will benefit from this new tool.

In addition to scientists who catalog brain cell types and behaviors, the technique is exciting for those studying when information storage goes awry—like in Alzheimer's disease.

In years to come, researchers around the world could use this technique to make exciting discoveries about the human brain's ability to learn new skills, remember day-to-day actions, and store information short- and long-term.

More information: Mohammad Samavat et al, Synaptic Information Storage Capacity Measured With Information Theory, *Neural Computation* (2024). DOI: 10.1162/neco_a_01659

Provided by Salk Institute

Research on how dietary choline travels through the blood-brain barrier reveals pathway for treating brain disorders

A University of Queensland researcher has found molecular doorways that could be used to help deliver drugs into the brain to treat neurological disorders.

Dr. Rosemary Cater from UQ's Institute for Molecular Bioscience led a team that discovered that an essential nutrient called choline is transported into the brain by a protein called FLVCR2. The research is published in *Nature*.

"Choline is a vitamin-like nutrient that is essential for many important functions in the body, particularly for brain development," Dr. Cater said.

"We need to consume 400–500 mg of choline per day to support cell regeneration, gene expression regulation, and for sending signals between neurons."

Dr. Cater said that until now, little was known about how dietary choline travels past the layer of specialized cells that separates the blood from the brain.

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"This blood-brain barrier prevents molecules in the blood that are toxic to the brain from entering," she said.

"The brain still needs to absorb nutrients from the blood, so the barrier contains specialized cellular machines—called transporters—that allow specific nutrients such as glucose, omega-3 fatty acids and choline to enter.

"While this barrier is an important line of defense, it presents a challenge for designing drugs to treat neurological disorders."

Dr. Cater was able to show that choline sits in a cavity of FLVCR2 as it travels across the blood-brain barrier and is kept in place by a cage of protein residues.

"We used high-powered cryo-electron microscopes to see exactly how choline binds to FLVCR2," she said.

"This is critical information for understanding how to design drugs that mimic choline so that they can be transported by FLVCR2 to reach their site of action within the brain.

"These findings will inform the future design of drugs for diseases such as Alzheimer's and stroke."

The research also highlights the importance of eating choline-rich foods—such as eggs, vegetables, meat, nuts and beans.

More information: Filippo Mancia, Structural and molecular basis of choline uptake into the brain by FLVCR2, *Nature* (2024). DOI: 10.1038/s41586-024-07326-y. www.nature.com/articles/s41586-024-07326-y

Provided by University of Queensland

Study discovers a 'brain thesaurus' that lets neurons derive meaning from spoken words

Using a novel technology for obtaining recordings from single neurons, a team of investigators at Massachusetts General Hospital, a founding member of the Mass General Brigham health care system, discovered a microscopic "thesaurus" that reflects how word meanings are represented by neurons in the human brain.

The research, which is published in *Nature*, opens the door to understanding how humans comprehend language and provides insights that could be used to help individuals with medical conditions that affect speech.

"Humans possess an exceptional ability to extract nuanced meaning through language—when we listen to speech, we can comprehend the meanings of up to tens of thousands of words and do so seamlessly across remarkably diverse concepts and themes," said senior author Ziv Williams, MD, a physician-

investigator in the department of Neurosurgery at Massachusetts General Hospital and an associate professor of Neurosurgery at Harvard Medical School.

"Yet, how the human brain processes language at the basic computational level of individual neurons has remained a challenge to understand."

Williams and his colleagues set out to construct a detailed map of how neurons in the human brain represent word meanings—for example, how we represent the concept of animal when we hear the word cat and dog, and how we distinguish between the concept of a dog and a car.

"We also wanted to find how humans are able to process such diverse meanings during natural speech and through which we are able to rapidly comprehend the meanings of words across a wide array of sentences, stories, and narratives," Williams said.

To start addressing these questions, the scientists used a novel technology that allowed them to simultaneously record the activities of up to a hundred neurons from the brain while people listened to sentences (such as, "the child bent down to smell the rose") and short stories (for example, about the life and times of Elvis Presley).

Using this new technique, the investigators discovered how neurons in the brain map words to particular meanings and how they distinguish certain meanings from others.

"For example, we found that while certain neurons preferentially activated when people heard words such as 'ran' or 'jumped,' which reflect actions, other neurons preferentially activated when hearing words that have emotional connotations, such as 'happy' or 'sad,'" said Williams.

"Moreover, when looking at all of the neurons together, we could start building a detailed picture of how word meanings are represented in the brain."

To comprehend language, though, it is not enough to only understand the meaning of words, but also to accurately follow their meanings within sentences. For example, most people can rapidly tell the correct meaning of words such as "sun" and "son" or "see" and "sea" when used in a sentence, even though the words sound exactly the same.

"We found that certain neurons in the brain are able to reliably distinguish between such words, and they continuously anticipate the most likely meaning of the words based on the sentence contexts in which they are heard," said Williams.

Lastly, and perhaps most excitingly, the researchers found that, by recording a relatively small number of brain neurons, they could reliably predict the meanings of words as they were heard in real-time during speech. That is, based on the activities of the neurons, the team could determine the general ideas and concepts experienced by an individual as they were being comprehended during speech.

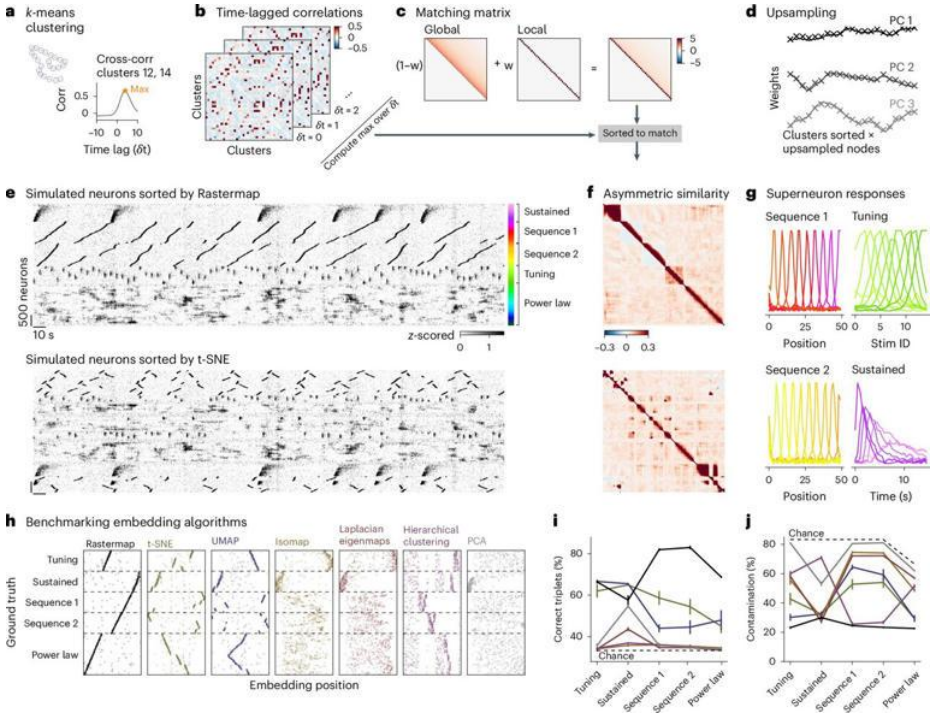
"By being able to decode word meaning from the activities of small numbers of brain cells, it may be possible to predict, with a certain degree of granularity, what someone is listening to or thinking," said Williams.

"It could also potentially allow us to develop brain-machine interfaces in the future that can enable individuals with conditions such as motor paralysis or stroke to communicate more effectively."

More information: Mohsen Jamali et al, Semantic encoding during language comprehension at single-cell resolution, *Nature* (2024). DOI: 10.1038/s41586-024-07643-2

Provided by Massachusetts General Hospital

Visualization tool helps scientists spot neuronal activity patterns in mountains of data



Benchmarking Rastermap on simulated data with multiplexed neural activity. Credit: Nature Neuroscience (2024). DOI: 10.1038/s41593-024-01783-4

Neuroscientists have learned a lot—like which neurons and circuits are associated with different behaviors—by recording the activity of small sets of neurons.

But what happens when you record thousands of neurons at one time? Or when you want to figure out the role of neurons when there isn't an obvious external catalyst or you're not sure what you're even looking for?

That's where Rastermap comes in.

The new visualization tool developed by the Stringer and Pachitariu labs at HHMI's Janelia Research Campus helps scientists uncover activity patterns in

large-scale neural recordings—the first step in the development of new theories about how individual neurons and circuits enable behavior.

The work is published in the journal *Nature Neuroscience*.

"If you want to explore your data, you need to visualize it," says Janelia Group Leader Carsen Stringer. "There are things you wouldn't necessarily think of that could be in that data, so you want to visualize it in a way to generate new hypotheses that you haven't thought of before."

Rastermap is an algorithm to sort the activity of thousands of neurons into clusters based on how similar their activity is, even if they are firing at different times or their activities don't match up with an observable behavior. The clusters are then mapped onto a raster plot, a graphical representation of the spikes over time, which allows researchers to visualize and identify patterns in the data that can then be further tested in the lab.

Unlike previous visualization tools, which use an average of the neuronal activity observed during many experimental trials to find patterns, Rastermap enables researchers to visualize neuronal activity from a single trial of an experiment. This allows them to see patterns in the data that couldn't be easily observed with previous methods. Rastermap also lets researchers observe neuronal activity patterns when there's no external stimulation.

So far, Rastermap, which has an easy-to-use graphical interface, has helped researchers visualize neuronal activity in flies, zebrafish, mice, rats, and primates.

"You can't ask an animal what they are thinking about, but you can use this unsupervised technique to discover potentially new things in your data that are related to the cognitive processes going on in the animal," Stringer says. Even if the activity is related to an external factor, "Rastermap helps you visualize it in a clearer way."

More information: Carsen Stringer et al, Rastermap: a discovery method for neural population recordings, *Nature Neuroscience* (2024). DOI: 10.1038/s41593-024-01783-4

Provided by Howard Hughes Medical Institute

A new approach to neuroimaging analysis

A group of neuroscientists based at University of California San Diego School of Medicine has applied an approach to neuroimaging that they believe will reinvigorate the work of many of their fellow brain researchers.

Their work, published in the journal *Cerebral Cortex*, outlines a method for the use of neuroimaging data to predict elements of cognition and behavioral variables. The technique involves examining widely used magnetic resonance images (MRIs) of brains to find associations to various behaviors, and then applying predictions from those associations to an independent unseen sample.

Carolina Makowski, Ph.D., a postdoctoral fellow in the Department of Radiology at UC San Diego School of Medicine, explains that researchers commonly use MRIs to examine specific structures of the brain to determine their role in behaviors or abilities including short-term memory, problem-solving ability or a wide range of cognitive functions.

Makowski, the first and corresponding author on the paper, said the group's work shows a way around a commonly held belief that neuroimaging studies couldn't yield meaningful results unless the study included thousands of participants.

"It's not always possible to have thousands of individuals," said Makowski. "There are so many studies and grants that are based on smaller datasets."

The study team found that the proper use of multivariate methods yielded satisfactory results with studies involving as few as a couple dozen participants. According to Makowski, typical neuroimaging studies operate from univariate analyses, which test a correlation or association between one point in the brain and one behavior. "In that case, yes, you may need thousands of participants in the study."

She explains that multivariate studies take in a pattern of associations. Additionally, Makowski said the group saw the largest effects of correlation and association by focusing on the task-based functional MRI data. "This was particularly strong for a task that taps into working memory processes," she said.

"Those task-activation patterns were predictive of general cognition, but also of relevant behavior that is actually part of the task."

Co-author Terry L. Jernigan, Ph.D., professor of cognitive science, psychiatry and radiology at UC San Diego and the director of the Center for Human Development, added that the team was able to get good results from smaller data sets by "training and tuning" large data sets using multivariate analysis methods. For training, the team used the Adolescent Brain Cognitive Development (ABCD) study database, a compendium of MRIs from some 12,000 nine- and ten-year olds.

"When there are a lot of especially well-structured data that are relevant to complex outcomes that we hope to predict, we can use multivariate methods—which are often referred to as AI by the way—to 'train' a large dataset," Jernigan said. She added that "tuning" of select relationships in a large dataset sharpens the predictive power when applied to smaller studies.

Makowski added that in general, the larger the training sample, the smaller the actual study can be, but even the training sample does not necessarily need to include thousands of individuals if you are working with strong effects to begin with.

"So, in predicting general cognition, if you have 5,000 children in the training sample, you can predict cognition from working-memory related brain activation with just 40 kids in the replication. Even at 100 kids in the training sample, we were still able to predict cognition pretty well with just 60 kids in the replication using these same brain activation patterns," she said.

Senior and co-corresponding author Anders M. Dale, Ph.D., professor of neurosciences, psychiatry, and cognitive science and data science at UC San Diego, said the group's method will help scientists tap the full potential of the ABCD database by enabling them to focus on smaller segments of the mammoth study relevant for different health outcomes.

"There is a reason the ABCD was so large in the first place," he said. "It was really because you wanted to be able to look at effects in a subset of individuals. We want to look at things like substance use outcomes, psychiatric outcomes, dementia. That's why it was designed that way."

Dale added that the predictive power of the small-sample approach can be amplified when it's supplemented by other types of analyses, such as genetics studies or other types of imaging.

Co-author Tim Brown, Ph.D., a researcher in the Department of Neurosciences, said the group's publication is important in that it reopens doors that brain researchers around the world believed had been slammed shut by a 2022 paper that asserted only very large databases could generate valuable results.

"You have a whole bunch of grant holders who don't have thousands of individuals in their studies," he said. "And they're suddenly being told: 'You can't do reproducible work.' What we're showing here is that reproducible brain-wide association studies do not require thousands of individuals."

More information: Carolina Makowski et al, Leveraging the adolescent brain cognitive development study to improve behavioral prediction from neuroimaging in smaller replication samples, *Cerebral Cortex* (2024). DOI: 10.1093/cercor/bhae223

Provided by University of California - San Diego

Ultra-thin wonder material absorbs 99% electromagnetic waves with ease

Scientists have developed a new material: an ultra-thin film that can absorb over 99% of electromagnetic waves.

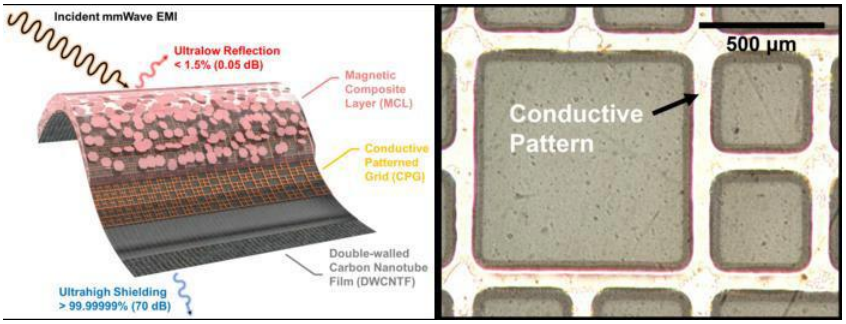
The Korea Institute of Materials Science (KIMS) states it to be the “world’s first ultra-thin film composite material capable of absorbing over 99% of electromagnetic waves.”

This material is less than half a millimeter thick, but it can effectively shield against a wide range of frequencies, including those used by 5G, 6G, Wi-Fi, and autonomous vehicle radar.

Unlike traditional shielding materials that reflect electromagnetic waves, this new material absorbs them, minimizing interference and improving the performance of electronic devices.

"As the applications of 5G/6G communications continue to expand, the importance of electromagnetic wave absorption and shielding materials is growing," said Byeongjin Park, senior researcher of KIMS, who led the development.

Park added: "This material has the potential to significantly improve the reliability of wireless communication devices such as smartphones and autonomous vehicle radars."



A conceptual diagram of the electromagnetic wave absorption and shielding material developed by the research team, along with the designed conductive pattern. Korea Institute of Materials Science (KIMS)

Need for new material

Electronic devices can emit waves that mess with other nearby devices, resulting in performance degradation.

These invisible waves can lead to glitches, signal loss, and even safety hazards.

Electromagnetic shielding materials are employed to mitigate this interference. These materials hold the potential to absorb the waves, which is said to be more effective than just reflecting them.

Conventional shielding materials primarily reflect electromagnetic waves, absorbing only a small fraction of 10%. Additionally, materials with higher absorption rates are often limited to a single frequency band.

To fix these problems, the team made a new material that can absorb waves from many different frequencies at the same time.

99% absorption

The material is super thin, bendy, and tough. It can bend without breaking, making it great for rollable phones and wearable tech.

“The team synthesized a magnetic material by altering the crystal structure of ferrite, enabling it to selectively absorb desired frequencies,” the press release noted.

They then combined this material with a thin polymer film and added conductive patterns to control wave propagation.

Finally, a carbon nanotube film was added to further improve the material’s shielding properties.

“This electromagnetic wave absorption and shielding material is less than 0.5mm thick and is distinguished by its low reflectance of less than 1% and high absorbance of over 99% across three different frequency bands,” the press release added.

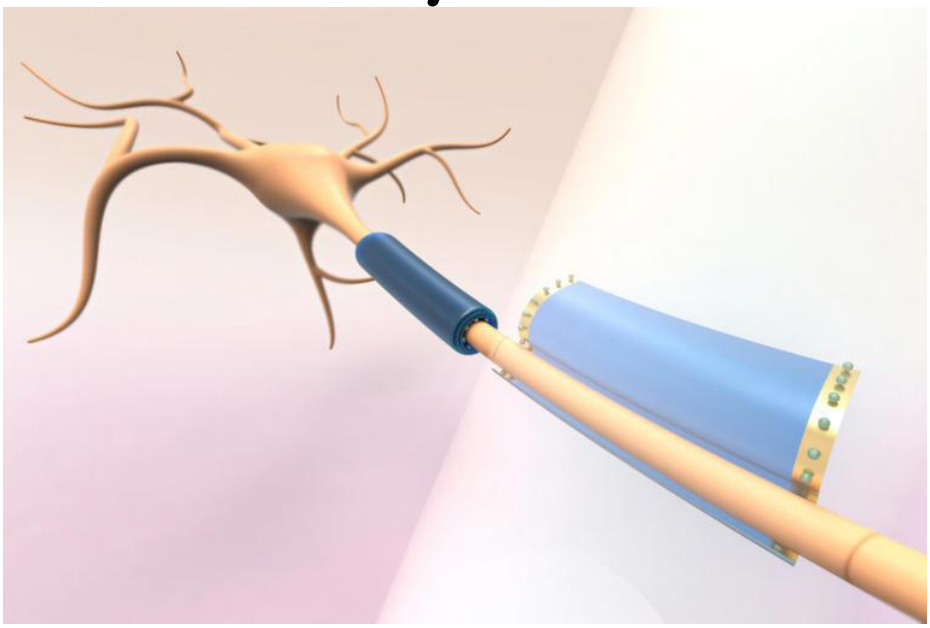
The research was supported by KIMS and the National Research Council of Science & Technology. The team has secured patents domestically and internationally and has licensed the technology to several companies for use in real-world applications, including communication devices and automobiles.

The findings were published in the journal *Advanced Functional Materials*.

The revolution of millimeter-wave (mmWave) technologies is prompting a need for absorption-dominant EMI shielding materials. While conventional shielding materials struggle in the mmWave spectrum due to their reflective nature, this study introduces a novel EMI shielding

film with ultralow reflection (<0.05 dB or 1.5%), ultrahigh absorption (>70 dB or 98.5%), and superior shielding (>70 dB or 99.99999%) across triple mmWave frequency bands with a thickness of 400 μm. By integrating a magnetic composite layer (MCL), a conductive patterned grid (CPG), and a double-walled carbon nanotube film (DWCNTF), specific resonant frequencies of electromagnetic waves are transmitted into the film with minimized reflection, and trapped and dissipated between the CPG and the DWCNTF. The design factors for resonant frequencies, such as the CPG geometry and the MCL refractive index, are systematically investigated based on electromagnetic wave propagation theories. This innovative approach presents a promising solution for effective mmWave EMI shielding materials, with implications for mobile communication, radar systems, and wireless gigabit communication.

Subcellular 'wearable' devices that wrap around neurons could measure and modulate electrical activity



This image shows the researchers' subcellular-sized devices, which are designed to gently wrap around different parts of neurons, such as axons and dendrites, without damaging the cells. The devices could be used to measure or modulate a neuron's electrical activity. Credit: Pablo Penso, Marta Airaghi

Wearable devices like smartwatches and fitness trackers interact with parts of our bodies to measure and learn from internal processes, such as our heart rate or sleep stages.

Now, MIT researchers have developed wearable devices that may be able to perform similar functions for individual cells inside the body.

These battery-free, subcellular-sized devices, made of a soft polymer, are designed to gently wrap around different parts of neurons, such as axons and dendrites, without damaging the cells, upon wireless actuation with light. By snugly wrapping neuronal processes, they could be used to measure or modulate a neuron's electrical and metabolic activity at a subcellular level.

Because these devices are wireless and free-floating, the researchers envision that thousands of tiny devices could someday be injected and then actuated noninvasively using light. Researchers would precisely control how the wearables gently wrap around cells, by manipulating the dose of light shined from outside the body, which would penetrate the tissue and actuate the devices.

By enfolding axons that transmit electrical impulses between neurons and to other parts of the body, these wearables could help restore some neuronal degradation that occurs in diseases like multiple sclerosis. In the long run, the devices could be integrated with other materials to create tiny circuits that could measure and modulate individual cells.

"The concept and platform technology we introduce here is like a founding stone that brings about immense possibilities for future research," says Deblina Sarkar, the AT&T Career Development Assistant Professor in the MIT Media Lab and Center for Neurobiological Engineering, head of the Nano-Cybernetic Biotrek Lab, and the senior author of a paper on this technique.

Sarkar is joined on the paper by lead author Marta J. I. Airaghi Leccardi, a former MIT postdoc who is now a Novartis Innovation Fellow; Benoît X. E. Desbiolles, an MIT postdoc; Anna Y. Haddad '23, who was an MIT undergraduate researcher during the work; and MIT graduate students Baju C. Joy and Chen Song. The research is published in *Communications Chemistry*.

Snugly wrapping cells

Brain cells have complex shapes, which makes it exceedingly difficult to create a bioelectronic implant that can tightly conform to neurons or neuronal processes. For instance, axons are slender, tail-like structures that attach to the cell body of neurons, and their length and curvature vary widely.

At the same time, axons and other cellular components are fragile, so any device that interfaces with them must be soft enough to make good contact without harming them.

To overcome these challenges, the MIT researchers developed thin-film devices from a soft polymer called azobenzene, that don't damage cells they enfold.

Due to a material transformation, thin sheets of azobenzene will roll when exposed to light, enabling them to wrap around cells. Researchers can precisely control the direction and diameter of the rolling by varying the intensity and polarization of the light, as well as the shape of the devices.

The thin films can form tiny microtubes with diameters that are less than a micrometer. This enables them to gently, but snugly, wrap around highly curved axons and dendrites.

"It is possible to very finely control the diameter of the rolling. You can stop when you reach a particular dimension you want by tuning the light energy accordingly," Sarkar explains.

The researchers experimented with several fabrication techniques to find a process that was scalable and wouldn't require the use of a semiconductor clean room.

Making microscopic wearables

They begin by depositing a drop of azobenzene onto a sacrificial layer composed of a water-soluble material. Then the researchers press a stamp onto the drop of polymer to mold thousands of tiny devices on top of the sacrificial layer. The stamping technique enables them to create complex structures, from rectangles to flower shapes.

A baking step ensures all solvents are evaporated and then they use etching to scrape away any material that remains between individual devices. Finally, they dissolve the sacrificial layer in water, leaving thousands of microscopic devices freely floating in the liquid.

Once they have a solution with free-floating devices, they wirelessly actuated the devices with light to induce the devices to roll. They found that free-floating structures can maintain their shapes for days after illumination stops.

The researchers conducted a series of experiments to ensure the entire method is biocompatible.

After perfecting the use of light to control rolling, they tested the devices on rat neurons and found they could tightly wrap around even highly curved axons and dendrites without causing damage.

"To have intimate interfaces with these cells, the devices must be soft and able to conform to these complex structures. That is the challenge we solved in this work. We were the first to show that azobenzene could even wrap around living cells," she says.

Among the biggest challenges they faced was developing a scalable fabrication process that could be performed outside a clean room. They also iterated on the ideal thickness for the devices, since making them too thick causes cracking when they roll.

Because azobenzene is an insulator, one direct application is using the devices as synthetic myelin for axons that have been damaged. Myelin is an insulating layer that wraps axons and allows electrical impulses to travel efficiently between neurons.

In non-myelinating diseases like multiple sclerosis, neurons lose some insulating myelin sheets. There is no biological way of regenerating them. By acting as synthetic myelin, the wearables might help restore neuronal function in MS patients.

The researchers also demonstrated how the devices can be combined with optoelectrical materials that can stimulate cells. Moreover, atomically thin materials can be patterned on top of the devices, which can still roll to form microtubes without breaking. This opens up opportunities for integrating sensors and circuits in the devices.

In addition, because they make such a tight connection with cells, one could use very little energy to stimulate subcellular regions. This could enable a researcher or clinician to modulate electrical activity of neurons for treating brain diseases.

"It is exciting to demonstrate this symbiosis of an artificial device with a cell at an unprecedented resolution. We have shown that this technology is possible," Sarkar says.

In addition to exploring these applications, the researchers want to try functionalizing the device surfaces with molecules that would enable them to target specific cell types or subcellular regions.

More information: Marta J. I. Airaghi Leccardi et al, Light-induced rolling of azobenzene polymer thin films for wrapping subcellular neuronal structures, *Communications Chemistry* (2024). DOI: 10.1038/s42004-024-01335-8

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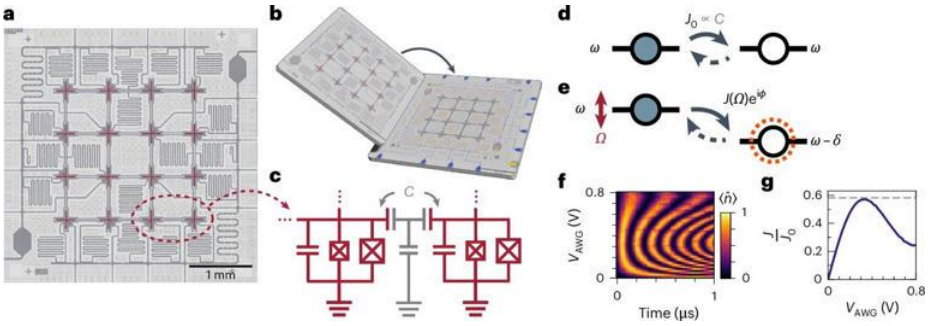
Provided by Massachusetts Institute of Technology

Quantum simulator could help uncover materials for high-performance electronics



Generating Peierls phases using parametric coupling in a 16-qubit superconducting processor. Credit: Nature Physics (2024). DOI: 10.1038/s41567-024-02661-3

Quantum computers hold the promise to emulate complex materials, helping researchers better understand the physical properties that arise from interacting atoms and electrons. This may one day lead to the discovery or design of better semiconductors, insulators, or superconductors that could be used to make ever faster, more powerful, and more energy-efficient electronics.

But some phenomena that occur in materials can be challenging to mimic using quantum computers, leaving gaps in the problems that scientists have explored with quantum hardware.

To fill one of these gaps, MIT researchers developed a technique to generate synthetic electromagnetic fields on superconducting quantum processors. The team has demonstrated the technique on a processor comprising 16 qubits.

Their work is published in the journal *Nature Physics*.

By dynamically controlling how the 16 qubits in their processor are coupled to one another, the researchers were able to emulate how electrons move between atoms in the presence of an electromagnetic field. Moreover, the synthetic electromagnetic field is broadly adjustable, enabling scientists to explore a range of material properties.

Emulating electromagnetic fields is crucial to fully exploring the properties of materials. In the future, this technique could shed light on key features of electronic systems, such as conductivity, polarization, and magnetization.

"Quantum computers are powerful tools for studying the physics of materials and other quantum mechanical systems. Our work enables us to simulate much more of the rich physics that has captivated materials scientists," says Ilan Rosen, an MIT postdoc and lead author of a paper on the quantum simulator.

The study's senior author is William D. Oliver, the Henry Ellis Warren professor of electrical engineering and computer science and of physics, director of the Center for Quantum Engineering, leader of the Engineering Quantum Systems group, and associate director of the Research Laboratory of Electronics. Oliver and Rosen are joined by others in the departments of Electrical Engineering and Computer Science and of Physics and at MIT Lincoln Laboratory.

A quantum emulator

Companies like IBM and Google are striving to build large-scale digital quantum computers that hold the promise of outperforming their classical counterparts by running certain algorithms far more rapidly.

But that's not all quantum computers can do. The dynamics of qubits and their couplings can also be carefully constructed to mimic the behavior of electrons as they move among atoms in solids.

"That leads to an obvious application, which is to use these superconducting quantum computers as emulators of materials," says Jeffrey Grover, a research scientist at MIT and co-author on the paper.

Rather than trying to build large-scale digital quantum computers to solve extremely complex problems, researchers can use the qubits in smaller-scale quantum computers as analog devices to replicate a material system in a controlled environment.

"General-purpose digital quantum simulators hold tremendous promise, but they are still a long way off. Analog emulation is another approach that may yield useful results in the near-term, particularly for studying materials. It is a straightforward and powerful application of quantum hardware," explains Rosen. "Using an analog quantum emulator, I can intentionally set a starting point and then watch what unfolds as a function of time."

Despite their close similarity to materials, there are a few important ingredients in materials that can't be easily reflected on quantum computing hardware. One such ingredient is a magnetic field.

In materials, electrons "live" in atomic orbitals. When two atoms are close to one another, their orbitals overlap and electrons can "hop" from one atom to another. In the presence of a magnetic field, that hopping behavior becomes more complex.

On a superconducting quantum computer, microwave photons hopping between qubits are used to mimic electrons hopping between atoms. But, because photons are not charged particles like electrons, the photons' hopping behavior would remain the same in a physical magnetic field.

Since they can't just turn on a magnetic field in their simulator, the MIT team employed a few tricks to synthesize the effects of one instead.

Tuning up the processor

The researchers adjusted how adjacent qubits in the processor were coupled to each other to create the same complex hopping behavior that electromagnetic fields cause in electrons.

To do that, they slightly changed the energy of each qubit by applying different microwave signals. Usually, researchers will set qubits to the same energy so that photons can hop from one to another. But for this technique, they dynamically varied the energy of each qubit to change how they communicate with each other.

By precisely modulating these energy levels, the researchers enabled photons to hop between qubits in the same complex manner that electrons hop between atoms in a magnetic field. In addition, because they can finely tune the microwave signals, they can emulate a range of electromagnetic fields with different strengths and distributions.

The researchers undertook several rounds of experiments to determine what energy to set for each qubit, how strongly to modulate them, and the microwave frequency to use.

"The most challenging part was finding modulation settings for each qubit so that all 16 qubits work at once," Rosen says.

Once they arrived at the right settings, they confirmed that the dynamics of the photons uphold several equations that form the foundation of electromagnetism. They also demonstrated the "Hall effect," a conduction phenomenon that exists in the presence of an electromagnetic field.

These results show that their synthetic electromagnetic field behaves like the real thing.

Moving forward, they could use this technique to precisely study complex phenomena in condensed matter physics, such as phase transitions that occur when a material changes from a conductor to an insulator.

"A nice feature of our emulator is that we need only change the modulation amplitude or frequency to mimic a different material system. In this way, we can

scan over many material properties or model parameters without having to physically fabricate a new device each time." says Oliver.

While this work was an initial demonstration of a synthetic electromagnetic field, it opens the door to many potential discoveries, Rosen says.

"The beauty of quantum computers is that we can look at exactly what is happening at every moment in time on every qubit, so we have all this information at our disposal. We are in a very exciting place for the future," he adds.

More information: Ilan T. Rosen et al, A synthetic magnetic vector potential in a 2D superconducting qubit array, *Nature Physics* (2024). DOI: 10.1038/s41567-024-02661-3

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Provided by Massachusetts Institute of Technology

Human proteins may explain inter-individual differences in functional brain connectivity, research suggests

A longstanding goal of neuroscience is to understand how molecules and cellular structures on a microscale give rise to communication between brain regions at the macroscale.

A study, titled "Multiscale Integration Identifies Synaptic Proteins Associated with Human Brain Connectivity," and published in *Nature Neuroscience* now identifies, for the first time, hundreds of brain proteins that explain inter-individual differences in functional connectivity and structural covariation in the human brain.

"A central goal of neuroscience is to develop an understanding of the brain that ultimately describes the mechanistic basis of human cognition and behavior," said Jeremy Herskowitz, Ph.D., associate professor in the University of Alabama at Birmingham Department of Neurology and co-corresponding author of the study with Chris Gaiteri, Ph.D., SUNY Upstate Medical University, Syracuse, New York.

"This study demonstrates the feasibility of integrating data from vastly different biophysical scales to provide a molecular understanding of human brain connectivity."

Bridging the gap from the molecular scale of proteins and mRNA to the brain-wide neuroimaging scale of functional and structural magnetic resonance imaging—a span of about seven orders of magnitude—was made possible by the Religious Orders Study and Rush Memory and Aging Project, or ROSMAP, at Rush University, Chicago, Illinois.

ROSMAP enrolls Catholic nuns, priests and brothers age 65 or older, who are without known dementia at time of enrollment. Participants receive medical and psychological evaluations each year and agree to donate their brains after death.

Herskowitz, Gaiteri and colleagues studied postmortem brain samples and data from a unique cohort of 98 ROSMAP participants. Their data types included resting state fMRI, structural MRI, genetics, dendritic spine morphometry, proteomics and gene expression measurements from the superior frontal gyrus and inferior temporal gyrus of the brain.

"Based on the stability of functional connectivity patterns within individuals, we hypothesized that it is possible to combine postmortem molecular and subcellular data with antemortem neuroimaging data from the same individuals to prioritize molecular mechanisms underlying brain connectivity," Herskowitz said.

The average age of the ROSMAP participants at time of MRI scan and at death were 88 +/- 6 years and 91 +/- 6 years, respectively, with an average time interval between the MRI scan and age at death of 3 +/- 2 years. The average postmortem interval to brain sampling was 8.5 +/- 4.6 hours. In the study, the researchers performed detailed characterization of each omic, cellular and neuroimaging data type, then integrated the different data types using computational clustering algorithms.

The key to the research was using an intermediate scale measurement—dendritic spine morphometry, the shapes, sizes and densities of the spines—to link the molecular scale with the brain-wide neuroimaging scale.

The integration of dendritic spine morphometry to contextualize the proteomic and transcriptomic signals was critical for detecting protein association with functional connectivity.

"Initially, the protein and RNA measures could not explain the person-to-person variability in functional connectivity; however, it all clicked once we integrated the dendritic spine morphology to bridge the gap from molecules to inter-brain region communication," Herskowitz said.

A dendrite is a branched extension from a neuron body that receives impulses from other neurons. Each dendrite can have thousands of small protrusions called spines. The head of each spine can form a contact point called a synapse to receive an impulse sent from the axon of another neuron.

Dendritic spines can rapidly change shape or volume while forming new synapses, part of the process called brain plasticity, and the head of the spine structurally supports postsynaptic density. Spines can be divided into shape subclasses based on their three-dimensional structure, such as thin, mushroom, stubby or filopodia.

This summer, in a different study, Herskowitz and colleagues used ROSMAP samples to show that preservation of memory in the very old was maintained by the quality, as measured by dendritic spine head diameter, not the quantity of synapses in the brain.

In this latest study, the hundreds of proteins the researchers identified that explain inter-individual differences in functional connectivity and structural covariation were enriched for proteins involved in synapses, energy metabolism and RNA processing.

"By integrating data at the genetic, molecular, subcellular and tissue levels, we linked specific biochemical changes at synapses to connectivity between brain regions," Herskowitz said.

"Overall, this study indicates that acquiring data across the major perspectives in human neuroscience from the same set of brains is foundational for understanding how human brain function is supported at multiple biophysical scales," Herskowitz said.

"While future research is necessary for fully determining the scope and components of multi-scale brain synchrony, we have established a robustly defined initial set of molecules whose effects likely resonate across biophysical scales."

More information: Multiscale Integration Identifies Synaptic Proteins Associated with Human Brain Connectivity, *Nature Neuroscience* (2024). DOI: 10.1038/s41593-024-01788-z

Provided by University of Alabama at Birmingham

Neuroscience research leverages stem cells to understand how neurons connect and communicate in the brain

Human neurons derived from stem cells by Assistant Professor Soham Chanda and his team at Colorado State University. Credit: Colorado State University© Provided by Medical Xpress

Newly published research from Colorado State University answers fundamental questions about cellular connectivity in the brain that could be useful in the development of treatments for neurological diseases like autism, epilepsy or schizophrenia.

The work, highlighted in the *Proceedings of the National Academy of Sciences,* focuses on how neurons in the brain transmit information between each other through highly specialized subcellular structures called synapses. These delicate structures are key to controlling many processes across the nervous

system via electrochemical signaling, and pathogenic mutations in the genes that impair their development can cause severe mental disorders.

Despite their important role in linking neurons across different brain regions, the way synapses form and function is still not well understood, said Assistant Professor Soham Chanda.

To answer that fundamental question, Chanda and his team in the Department of Biochemistry and Molecular Biology focused on a specific and important type of synapse called GABAergic. He said neuroscience researchers have long hypothesized that these synapses might form because of a release of GABA and the corresponding sensing activity between two neurons in proximity. However, research in the paper now shows that these synapses can begin to develop autonomously and apart from that neuronal communication, mainly due to the scaffolding action of a protein called Gephyrin. These findings clarify the key mechanisms of synaptic formation, which might allow researchers to further focus on synapse dysfunction and health treatment options.

Chanda's team used human neurons derived from stem cells to develop a model of the brain that could rigorously test these relationships. Using a gene-editing tool called CRISPR-Cas9, they were able to genetically manipulate the system and confirm the role of Gephyrin in the synapse formation process.

"Our study shows that even if a pre-synaptic neuron is not releasing GABA, the post-synaptic neuron can still put together the necessary molecular machineries prepared to sense GABA," Chanda said. "We used a gene-editing tool to remove the Gephyrin protein from neurons, which largely reduced this autonomous assembly of synapses—confirming its important role irrespective of neuronal communication."

Using stem cells to advance understanding of neuron and synapse formation

Neuroscientists have traditionally used rodent systems to study these synaptic connections in the brain. While that provides a suitable model, Chanda and his

team were interested in testing synapse properties in a human cellular environment that could eventually be more easily translated into treatments.

To achieve this, his team cultivated human stem cells to form brain cells that could mimic the properties of human neurons and synapses. They then conducted extensive high-resolution imaging of these neurons and tracked their electrical activities to understand synaptic mechanisms.

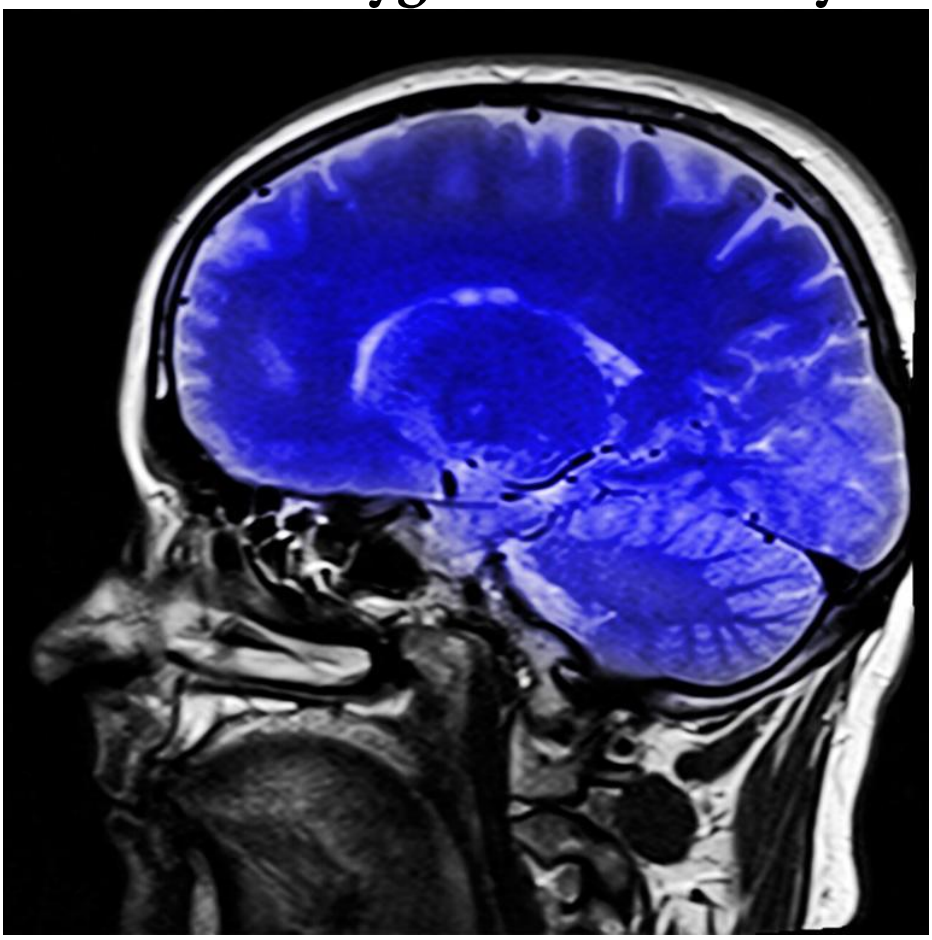
Chanda said that several mutations in the Gephyrin protein have been associated with neurological disorders like epilepsy, which alters neuronal excitability in the human brain. That makes understanding its basic cellular function an important first step towards treatment and prevention.

"Now that we better understand how these synaptic structures interact and organize, the next question will be to elucidate how defects in their relationships can lead to disease and identify the ways one can predict or intervene in that process," he said.

More information: Etta Carricaburu et al, Gephyrin promotes autonomous assembly and synaptic localization of GABAergic postsynaptic components without presynaptic GABA release, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2315100121

Provided by Colorado State University

The roots of fear: Scientists identify new cell clusters in amygdala for anxiety treatment



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Treating anxiety, depression and other disorders may depend on the amygdala, a part of the brain that controls strong emotional reactions, especially fear. But a deep understanding of this structure has been lacking. Now scientists at the University of California, Davis have identified new clusters of cells with differing patterns of gene expression in the amygdala of humans and non-human primates. The work could lead to more targeted treatments for disorders such as anxiety that affect tens of millions of people.

The work is published in the *American Journal of Psychiatry*.

"The amygdala is central to emotion processing in the brain, and is known to contribute to fear and anxiety," said Drew Fox, associate professor in the UC Davis Department of Psychology and senior author on the paper.

For that reason, there has long been interest in whether variations in the size or structure of the amygdala are related to disorders such as anxiety and depression. However, it's increasingly clear that the overall size and structure of the amygdala is not a good predictor of emotional problems in life, Fox said.

Recently, research in rodents has shown that each subregion of the amygdala contains many different cell types with distinct and sometimes opposing functions.

"This suggests that disorders emerge from alterations in specific cell types with distinct roles," Fox said. However, it is challenging to identify such cell types in humans or other primates, leaving the cellular landscape of the primate amygdala largely unexplored.

To address this critical knowledge gap, graduate student Shawn Kamboj led a collaboration between Fox's research group and the lab of Professor Cynthia Schumann at the UC Davis School of Medicine to identify cell types in subregions of the human and non-human primate amygdala, based on the genes they express. This could advance basic research by making it easier to translate results between rodents, non-human primates and humans, and open up new targets for treatment.

Single cell RNA sequencing

The researchers took samples from brains of humans and rhesus macaque monkeys, separated individual cells and sequenced their RNA. This shows which genes are active (being expressed) in a particular cell and allows researchers to sort them into groups based on gene expression.

"We can cluster cells based on their gene expression, identify cell types and their developmental origin," Fox said.

The researchers searched for specific cell types that expressed the genes implicated in anxiety and other disorders in humans. This strategy can help identify cell types that are most likely to give rise to psychopathology, Fox said.

For example, they identified a specific group of cells that expressed a gene called FOXP2. The new study shows that in humans and macaques, FOXP2 is expressed in cells on the edges of the amygdala, called intercalated cells. Excitingly, researchers have demonstrated that in rodents, this small group of FOXP2-expressing cells play a role as "gatekeepers," controlling signal traffic in or out of the amygdala. Together, these data suggest intercalated cells to be a potentially powerful avenue for developing treatments.

The researchers were also able to identify both similarities and differences between cell types in the human and non-human primate amygdala. This is important for understanding how discoveries in animal models of disorders such as anxiety and autism relate to humans.

The approach could help identify cell types as potential drug targets. For example, FOXP2-expressing cells tend to express both anxiety-related genes and a receptor that can be targeted by drugs, called Neuropeptide FF Receptor 2 (NPFFR2). This result can guide the development of new treatment strategies, by suggesting drugs that activate the NPFFR2 pathway as a potential treatment target in relation to anxiety-related disorders.

Anxiety is a complicated disorder that can present in many different ways. With a better understanding of the cell types involved, it may be possible to identify and target "chokepoints" that affect large numbers of people who experience extreme and debilitating anxiety, Fox said.

"Put simply, if we're developing a drug to target the amygdala, we want to know which cell type we are targeting," he said.

More information: Shawn Kamboj et al, Translational Insights From Cell Type Variation Across Amygdala Subnuclei in Rhesus Monkeys and Humans, *American Journal of Psychiatry* (2024). DOI: 10.1176/appi.ajp.20230602

Provided by UC Davis

New algorithm disentangles intrinsic brain patterns from sensory inputs

Maryam Shanechi and her team have developed a new machine learning method that reveals surprisingly consistent intrinsic brain patterns across different subjects by disentangling these patterns from the effect of visual inputs. The work has been published in the *Proceedings of the National Academy of Sciences*.

When performing various everyday movement behaviors, such as reaching for a book, our brain has to take in information, often in the form of visual input—for example, seeing where the book is. Our brain then has to process this information internally to coordinate the activity of our muscles and perform the movement.

But how do millions of neurons in our brain perform such a task? Answering this question requires studying the neurons' collective activity patterns, but doing so while disentangling the effect of input from the neurons' intrinsic (aka internal) processes, whether movement-relevant or not.

That's what Shanechi, her Ph.D. student Parsa Vahidi, and a research associate in her lab, Omid Sani, did by developing a new machine-learning method that models neural activity while considering both movement behavior and sensory input.

"Prior methods for analyzing brain data have either considered neural activity and input but not behavior, or considered neural activity and behavior but not input," Shanechi said.

"We developed a method that can consider all three signals—neural activity, behavior, and input—when extracting hidden brain patterns. This allowed us to not only disentangle input-related and intrinsic neural patterns, but also separate out which intrinsic patterns were related to movement behavior and which were not."

Shanechi and her team used this method to study three publicly available datasets, during which three different subjects performed one of two distinct movement tasks, consisting of moving a cursor on a computer screen over a grid or moving it sequentially to random locations.

"When using methods that did not consider all three signals, the patterns found in neural activity of these three subjects looked different," Vahidi said. But when the team used the new method to consider all three signals, a remarkably consistent hidden pattern emerged from neural activity of all three subjects that was relevant to movement. This similarity was despite the fact that the tasks performed by the three subjects were also different.

"In addition to revealing this new consistent pattern, the method also improved the prediction of neural activity and behavior compared to when all three signals were not considered during machine learning, as in prior work," Sani said. "The new method enables researchers to more accurately model neural and behavioral data by accounting for various measured inputs to the brain, such as sensory inputs as in this work, electrical or optogenetic stimulation, or even input from different brain areas."

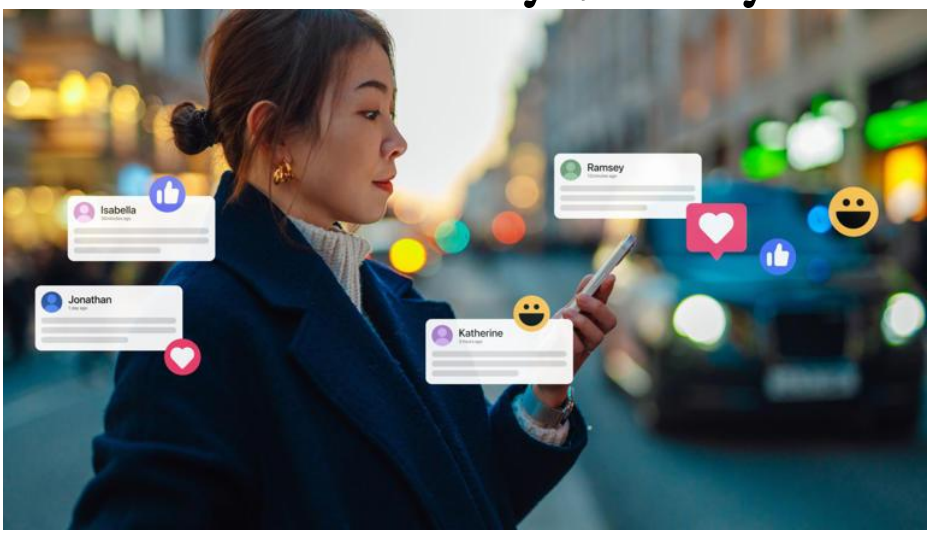
This method and the discovered pattern can help us understand how our brains perform movements, guided by the information we receive from the external world. Further, by modeling the effect of input and separating out intrinsic patterns that are behavior-relevant, this method can help develop future brain-computer interfaces that regulate abnormal brain patterns in disorders such as major depression by optimizing external inputs such as deep brain stimulation therapy.

"We are excited about how this algorithm could facilitate both scientific discoveries and the development of future neurotechnologies for millions of patients with neurological or neuropsychiatric disorders," Shanechi said.

More information: Parsa Vahidi et al, Modeling and dissociation of intrinsic and input-driven neural population dynamics underlying behavior, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2212887121

Provided by University of Southern California

Our brains can understand written sentences in the 'blink of an eye,' study reveals



Human brains can discern the basic structures of written language from a single glance — enabling us to quickly consume the torrent of information fed to us by smartphones, a new study finds.

By measuring the brain activity of 36 volunteers, scientists found that people can detect basic sentence structures in as little as 125 milliseconds, or about the speed of a blink of an eye.

This means that people can process words as quickly as we comprehend visual scenes, a skill that enables us to continually observe and navigate the world around us. The new finding, published Wednesday (Oct. 23) in the journal Science Advances, could help reveal key clues about how our brains encode language, the researchers said.

Studying how the brain processes written messages enables scientists to understand more about the properties of language — particularly those properties that are not linked to speech, Liina Pylkkanen, a professor of linguistics and psychology at New York University, told Live Science.

Studying the neurobiology of language is often made difficult by the mouth, in that it "forces us to turn the language into a sequence" of brain activity in order to speak words aloud, Pylkkänen said. This restricts our understanding of language's properties to those demanded by the word-by-word serialization needed for speech.

To sidestep this issue, the researchers used a non-invasive technique called magnetoencephalography, which uses magnetic fields to track electrical activity in the brain. While being scanned, volunteers were presented with a three-word sentence structure that flashed onto a screen for 300 ms, followed by a second set of words that was either left the same or altered by one word. The participants' task was to assess whether the second sentence was the same as the first or had been changed.

The scans revealed that the brain's left temporal cortex — part of the organ's outermost layer that's key for understanding language — showed higher activity for three-word sentences than unstructured lists of words, and this activity showed up in just 125 ms.

Participants performed their best when the sentences contained a subject, verb and object, with the fastest brain activity being seen for phrases such as "nurses clean wounds," compared to noun lists like "hearts lungs livers."

This rapid detection was also seen for sentences that contained agreement errors, in which the verb doesn't match the pluralization of the subject — for example, "nurses cleans wounds." The brain also quickly detected implausible sentences, such as "wounds clean nurses." The researchers said this suggests that our brains aren't just detecting the presence of the words but are applying our previous knowledge of the world to better parse what the sentences mean right away.

"So just like your own car is quickly identifiable in a parking lot, certain language structures are quickly identifiable and can then give rise to a rapid effect of syntax in the brain," Pylkkänen said. "It's interesting since the [sentence] structural knowledge is abstract, but somehow you're still able to grasp it from the stimulus."

The researchers plan to follow up on their findings by further studying the types of sentence structures that the brain can detect quickly, and by looking into whether these align with the types of sentences people first learn as children.

They also plan to study whether other visual stimuli, such as images, are processed using any of the same mechanisms we use to understand text.

Your native language may shape the wiring of your brain

The connections between different regions of the brain responsible for language processing depend on which language you grew up with.

A person's native language may shape how their brain builds connections between different hubs of information processing, a new brain scan study reveals.

The observed differences in these language network structures were related to linguistic characteristics in the native languages of the study participants: German and Arabic.

"So the difference we find there shouldn't be due to different ethnic background but really because of the language we [they] speak," Alfred Anwander, a researcher at the Max Planck Institute for Human Cognitive and Brain Sciences in Germany who led the study, told Live Science. The research was published online in February in the journal NeuroImage.
Although the language network grows to be one of the strongest networks in the brain, the connections at birth are weak. As we learn to speak, links strengthen between the various brain regions that are responsible for different types of language processing, such as recognizing words from sounds and interpreting the meaning of sentences, Anwander explained.

Different languages may tax some types of language processing more than others. The researchers wanted to see how these differences affect the formation of connections in the brain.

Previous studies had highlighted regions of the brain that activate during language processing. These are primarily situated in the left hemisphere, although both sides of the brain are invoked in auditory processing, and the region that assesses stress and intonation in the pronunciation of words lives in the right hemisphere.

Discussing the paper at a seminar, Patrick Friedrich, a researcher at the Institute for Neuroscience and Medicine at Forschungszentrum Jülich in Germany who was not

involved in the study, noted that the brain's language network is understood to be "more or less universal among participants of different native languages." Yet, scientists have observed differences in how the brain processes second languages. "I thought this study was really interesting because it shows for the first time a structural difference depending on the native experience," rather than languages learned later, Friedrich said.

The study included 94 participants. Half spoke only German, and the other half spoke only Arabic, having recently settled in Germany. Although they spoke different languages and grew up in different cultures, the participants were closely matched in terms of other factors that can influence brain wiring, such as age and education level.

Brain scans were obtained using "diffusion MRI," which tracks the directional mobility of water molecules to identify structures such as axons, which the water can move along easily.

The scans revealed that the native German speakers showed increased connectivity in the regions of the left hemisphere involved in language processing, compared with the Arabic speakers. Anwander noted that German is considered syntactically complicated, meaning the sense of a sentence is gleaned less from the word order and more from the grammatical forms of the words. Thus, words that depend on each other for their meaning may be at opposite ends of a sentence. Syntactic processing regions are mostly in frontal parts of the left hemisphere, so the higher connectivity within the left hemisphere makes sense, he said.
In contrast, Anwander described Arabic as semantically complex — while the sentence word order remains more fixed, the words' meanings can be more taxing to decode. The researchers observed increased connectivity between the left and right hemispheres for Arabic speakers that reflected this.

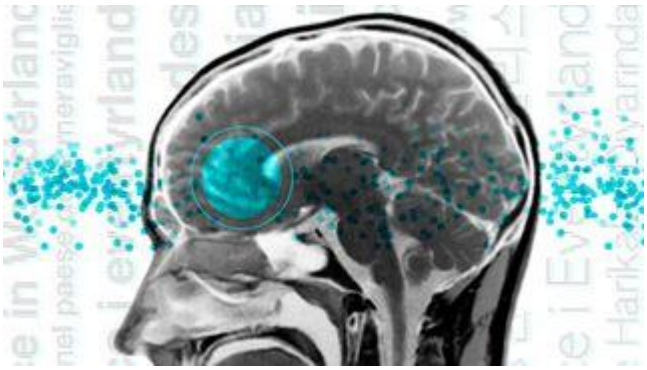
It's possible that the language network shaped by a person's first language might influence other nonlinguistic cognitive abilities, Anwander said. For example, a German speaker's memory might be influenced by their having to hear whole sentences before parsing their meaning.

David Green, an emeritus professor of psychology at University College London, described the work as "technically accomplished" but voiced reservations. Beyond the linguistic features of a language, cultural features of conversation, such as how people use gestures, may also shape brain networks, he told Live Science in an email.

The study also didn't cover all the brain regions involved in language processing, nor did it include measures of brain activity that could be compared across individuals. "We do need to grasp the variety of ways in which the brain may solve a given task and the nature of that variety across individuals," he said.

Nonetheless, Anwander sees potential for this line of research, and wonders whether it might be possible to predict the native language of an individual from a brain scan. He and his colleagues would like to extend the study to more languages, to find out.

'Universal language network' identified in the brain



The brain's language processing network is mostly located in the left hemisphere. (Image credit: Christine Daniloff, MIT; iStock image)

Japanese, Italian, Ukrainian, Swahili, Tagalog and dozens of other spoken languages cause the same "universal language network" to light up in the brains of native speakers. This hub of language processing has been studied extensively in English speakers, but now neuroscientists have confirmed that the exact same network is activated in speakers of 45 different languages representing 12 distinct language families.

"This study is very foundational, extending some findings from English to a broad range of languages," senior author Evelina Fedorenko, an associate professor of neuroscience at MIT and a member of MIT's McGovern Institute for Brain Research, said in a statement.
"The hope is that now that we see that the basic properties seem to be general across languages, we can ask about potential differences between languages and language families in how they are implemented in the brain, and we can

study phenomena that don't really exist in English," Fedorenko said. For example, speakers of "tonal" languages, such as Mandarin, convey different word meanings through shifts in their tone, or pitch; English isn't a tonal language, so it might be processed slightly differently in the brain.
The study, published Monday (July 18) in the journal Nature Neuroscience, included two native speakers of each language, who underwent brain scans as they performed various cognitive tasks. Specifically, the team scanned the participants' brains using a technique called functional magnetic resonance imaging (fMRI), which tracks the flow of oxygenated blood through the brain. Active brain cells require more energy and oxygen, so fMRI provides an indirect measure of brain cell activity.

During the fMRI scans, the participants listened to passages from Lewis Carroll's "Alice's Adventures in Wonderland" (better known as "Alice in Wonderland") read in their native languages. In theory, all of the listeners should use the same language network to process stories read in their native tongues, the researchers hypothesized.

The participants also listened to several recordings that, theoretically, wouldn't activate this language network. For example, they listened to recordings in which the native speaker's words were distorted beyond recognition and to passages read by a speaker of an unfamiliar language. In addition to completing these language-related tests, the participants were asked to do math problems and perform memory tasks; like the incoherent recordings, neither the math nor the memory tests should activate the language network, the team theorized.

"Language areas [of the brain] are selective," first author Saima Malik-Moraleda, a doctoral student in the Speech and Hearing Bioscience and Technology program at Harvard University, said in the statement. "They shouldn't be responding during other tasks, such as a spatial working memory task, and that was what we found across the speakers of 45 languages that we tested."

In native English speakers, the brain areas that activate during language processing appear mostly in the left hemisphere of the brain, primarily in the frontal lobe, located behind the forehead, and in the temporal lobe, located behind the ear. By constructing "maps" of brain activity from all their subjects,

the researchers revealed that these same brain areas activated regardless of the language being heard.

The team did observe slight differences in brain activity among the individual speakers of different languages. However, the same, small degree of variation has also been seen among native English speakers.

These results aren't necessarily surprising, but they lay a critical foundation for future studies, the team wrote in their report. "Although we expected this to be the case, this demonstration is an essential foundation for future systematic, in-depth and finer-grained cross-linguistic comparisons," they wrote.

Originally published on Live Science.

'Secret code' behind key type of memory revealed in new brain scans

The "secret code" the brain uses to create a key type of memory has finally been cracked.

This type of memory, called working memory, is what allows people to temporarily hold on to and manipulate information for short periods of time. You use working memory, for example, when you look up a phone number and then briefly remember the sequence of digits in order to dial, or when you ask a friend for directions to a restaurant and then keep track of the turns as you drive there.

The new work represents a "fundamental step forward" in the study of working memory, Derek Nee, an assistant professor of psychology and neuroscience at Florida State University, told Live Science in an email.

A critical process

For decades, scientists have wondered how and where the brain encodes transient memories.
One theory suggests that working memory relies on special "storehouses" in the brain, separate from where the brain handles incoming sensory information from the eyes or nose, for instance, or

where long-term memories — like memories of who you attended prom with, or foundational knowledge you learned in school — are stored, said Nee, who was not involved in the new study.
Another, opposing theory suggests that "there are no such special storehouses," Nee told Live Science. In this alternate theory, working memory is essentially an emergent phenomenon — one that shows up "when sensory and motor representations are kept around as we link the past to the future," Nee said. According to this theory, the same brain cells light up when you first read through a phone number as do when you run through that number again and again in working memory.

The new study, published April 7 in the journal Neuron, challenges both of these theories. Rather than reflecting what happens during perception or relying on special memory storehouses, working memory seems to operate one step up from sensory information gathering; it extracts only the most relevant sensory information from the environment and then sums up that information in a relatively simple code.
"There have been clues for decades that what we store in [working memory] might be different from what we perceive," study senior author Clayton Curtis, a professor of psychology and neural science at New York University (NYU), told Live Science in an email.

To solve the mysteries of working memory, Curtis and co-author Yuna Kwak, a doctoral student at NYU, used a brain scanning technique called functional magnetic resonance imaging (fMRI), which measures changes in blood flow to different parts of the brain. Active brain cells require more energy and oxygen, so fMRI provides an indirect measure of brain cell activity.

The team used this technique to scan the brains of nine volunteers while they performed a task that engaged their working memory; the two study authors also completed the task and contributed brain scans to the study.

In one of the trials, the participants viewed a circle composed of gratings, or slashes, on a screen for roughly four seconds; the graphic then disappeared, and 12 seconds later, the participants were asked to recall the angle of the slashes. In other trials, the participants viewed a cloud of moving dots that all shifted in the same direction, and they were asked to recall the exact angle of the dot cloud's motion.

"We predicted that participants would recode the complex stimulus" — the angled grating or moving dots — "into something more simple and relevant to the task at hand," Curtis told Live Science. Participants were only asked to pay attention to the orientation of the slashes or angle of the dot cloud's motion, so the researchers theorized that their brain activity would reflect only those specific attributes of the graphics.

And when the team analyzed the brain scan data, that's just what they found.

The researchers used computer modeling to visualize the complex brain activity, creating a kind of topographical map representing peaks and valleys of activity in different groups of brain cells. Brain cells that process visual data have a specific "receptive field," meaning they activate in response to stimuli that appear in a particular zone of a person's visual field. The team took these receptive fields into account in their models, which helped them understand how the participants' brain activity related to what they'd observed on-screen during the memory task.

This analysis revealed that, instead of encoding all of the fine details of each graphic, the brain stored only the relevant information needed for the task at hand. When viewed on the topographical maps, the brain activity used to encode this information looked like a simple, straight line. The angle of the line would match the orientation of the gratings or the angle of the dot cloud's motion, depending on which graphic the participants had been shown.

These line-like brain activity patterns appeared in the visual cortex, where the brain receives and processes visual information, and the parietal cortex, a key region for memory processing and storage.

What's crucial isn't that the brain settled on using lines to represent the images. "It is the fact that the representation has been abstracted from gratings [or] motion to something different," Nee said.

One limitation of the study is that the team used very simplistic graphics, which don't necessarily reflect the visual complexity of the real world, Nee noted. This limitation extends to many studies of working memory, and Nee said he uses similar simple graphics in his own research.

"The field will need to move towards richer stimuli that better match our natural visual experiences to bring us from the laboratory to practical utility," he said. But with that in mind, the new study still "provides a novel insight into what it means to hold something online in mind for the future," he said.

Working memory essentially acts as a bridge between perception (when we read a phone number) and action (when we dial that number). "This study, in identifying a representational format that resembles neither what was perceived nor what will be done but can be clearly read out from visual signals, offers an unprecedented look into this mysterious intermediate zone between perception and action," Nee said.

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Unique Brain Signal Just Discovered. And It Might Make Us 'Human'

A new study suggests that human neurons may have more computing power than once thought.

Cells nestled in the outermost layers of the human brain generate a special kind of electrical signal that might grant them an extra boost of computing power, new research suggests. What's more, this signal may be unique to humans — and may explain our unique intelligence, according to the study authors.

Brain cells, or neurons, link up through long, branching wires and shuttle messages along these cables to communicate with each other. Each neuron has both an outgoing wire, called an axon, and a wire that receives incoming messages, known as a dendrite. The dendrite passes on information to the rest of the neuron through bursts of electrical activity. Depending on how the brain is wired up, each dendrite may receive hundreds of thousands of signals from other neurons along its length. While scientists believe these electrical spikes help wire the brain and may underlie abilities like learning and memory, the exact role of dendrites in human cognition remains a mystery.
Now, researchers have uncovered a new flavor of electrical spike in human dendrites — one they think might allow the cells to perform computations once thought too complex for a single neuron to tackle on its own. The study, published Jan. 3 in the journal Science, notes that the newfound electrical property has never been observed in any animal tissue other than human, raising the question of whether the signal uniquely contributes to human intelligence, or to that of primates, our evolutionary cousins.

A strange signal

Up until now, most dendrite studies have been carried out in rodent tissue, which shares basic properties with human brain cells, said study co-author Matthew Larkum, a professor in the department of biology at Humboldt University in Berlin. However, human neurons measure about twice as long as those found in a mouse, he said.

"That means the electrical signals have to travel twice as far," Larkum told Live Science. "If there was no change in the electrical properties [between rodents and people], then that would mean that, in the

humans, the same synaptic inputs would be quite a bit less powerful." In other words, electrical spikes received by a dendrite would weaken significantly by the time they reached the cell body of the neuron. So Larkum and his colleagues set out to uncover the electrical properties of human neurons to see how these longer dendrites actually manage to send signals effectively.

This was no easy task.

First, the researchers had to get their hands on human brain tissue samples, a notoriously scarce resource. The team ended up using neurons that had been sliced from the brains of epilepsy and tumor patients as part of their medical treatment. The team focused on neurons resected from the cerebral cortex, the wrinkled exterior of the brain that contains several distinct layers. In humans, these layers hold dense networks of dendrites and grow to be extremely thick, an attribute that may be "fundamental to what makes us human," according to a statement from Science.
"You get the tissue very infrequently, so you've just got to work with what's in front of you," Larkum said. And you have to work fast, he added. Outside the human body, the oxygen-starved brain cells only remain viable for about two days. To take full advantage of this limited time window, Larkum and his team would gather measurements from a given sample for as long as they could, sometimes working for 24 hours straight.

During these experimental marathons, the team chopped brain tissue into slices and poked holes in the dendrites contained within. By sticking thin glass pipettes through these holes, the researchers could inject ions, or charged particles, into the dendrites and observe how they changed in electrical activity. As expected, the stimulated dendrites generated spikes of electrical activity, but these signals looked very different from any seen before.

Each spike ignited for only a brief period of time — about a millisecond. In rodent tissue, this type of supershort spike occurs when a flood of sodium enters a dendrite, triggered by a particular accumulation of electrical activity. Calcium can also trigger spikes in rodent dendrites, but these signals tend to last 50 to 100 times longer than sodium spikes, Larkum said. What the team saw in human tissue, though, seemed to be a strange hybrid of the two.

"Although it looked like a sodium event, it was actually a calcium event," Larkum said. The team members tested what would happen if they prevented sodium from entering their sample dendrites and found that the spikes continued to fire unabated. What's more, the supershort spikes fired in rapid succession, one right after the other. But when the researchers blocked calcium from entering the neurons, the spikes stopped short. The scientists concluded that they had stumbled upon a brand-new class of spike, one similar in duration to sodium but controlled by calcium.

"These [spikes] look different than whatever we have known so far from other mammals," said Mayank Mehta, a professor in the departments of neurology, neurobiology physics and astronomy at the University of California, Los Angeles, who was not involved in the study. The big question is, how do these spikes relate to actual brain function, he said.

Computational powerhouses

Larkum and his colleagues couldn't test how their sliced-up samples might behave in an intact human brain, so they engineered a computer model based on their results. In the brain, dendrites receive signals along their length from nearby neurons that can either push them to generate a spike or prevent them from doing so. Similarly, the team designed digital dendrites that can be stimulated or inhibited from thousands of different points along their lengths. Historically, studies suggest that dendrites tally up these opposing signals over time and

fire a spike when the number of excitatory signals outnumbers the inhibitory ones.

But the digital dendrites didn't behave this way at all.

"When we looked closely, we could see that there was this strange phenomenon," Larkum said. The more excitatory signals a dendrite received, the less likely it was to generate a spike. Instead, each region in a given dendrite seemed "tuned" to respond to a specific level of stimulation — no more, no less.

But what does this mean in terms of actual brain function? It means that dendrites may be processing information at each and every point along their lengths, working as a unified network to decide which information to send along, which to discard and which to handle alone, Larkum said.

"It doesn't look that the cell is just adding things up — it's also throwing things away," Mehta told Live Science. (In this case, the "throw away" signals would be excitatory signals that are not properly tuned to the dendritic region's "sweet spot.") This computational superpower could enable dendrites to take on functions once thought to be the work of whole neural networks; for instance, Mehta theorizes that individual dendrites could even encode memories.
Once, neuroscientists thought that whole networks of neurons worked together to perform these complex calculations and decided how to respond as a group. Now, it seems like an individual dendrite does this exact type of calculation all on its own.

It may be that only the human brain possesses this impressive computational power, but Larkum said that it's too early to say for sure. He and his colleagues want to search for this mysterious calcium spike in rodents, in case it has been overlooked in past research. He also hopes to collaborate on similar studies in primates to see if the

electrical properties of human dendrites are similar to those of our evolutionary relatives.

It is very unlikely that these spikes make humans special or more intelligent than other mammals, Mehta said. It may be that the newfound electrical property is unique to L2/3 neurons in the human cerebral cortex, as the rodent brain also produces specific spikes in particular regions of the brain, he added.

In past research, Mehta found that rodent dendrites also generate a wide variety of spikes whose exact function remains unknown. What's interesting is that only a fraction of these spikes actually trigger a reaction in the cell body they plug into, he said. In rodent neurons, roughly 90 percent of dendritic spikes don't prompt electrical signals from the cell body, suggesting that dendrites in both rodents and humans may be processing information independently, in ways we don't yet understand.
Much of our understanding of learning and memory stems from research on electrical activity generated in the neuron cell body and its output cable, the axon. But these findings suggest that "it may be that the majority of spikes in the brain may be taking place in the dendrites," Mehta said. "Those spikes could change the rules of learning.

We finally know why the brain uses so much energy

Your brain may be leaking ... energy, according to a new study that may explain why your noggin consumes 20% of the energy needed to keep your body running.

The study researchers found that tiny sacs called vesicles that hold messages being transmitted between brain cells may be constantly oozing energy, and that leakage is likely a trade-off for the brain being ready to fire at all times, according to a new study published Dec. 3 in the journal Science Advances.

"The brain is considered a very expensive organ to run," said senior author Timothy Ryan, a professor of biochemistry at Weill Cornell Medicine in New York City.
Scientists previously assumed this energy suck had to do with the fact that the brain is electrically active, which means that brain cells, or neurons, are constantly firing electrical signals to communicate, a process that burns large amounts of an energy molecule known as adenosine 5'-triphosphate (ATP).

But over the past couple of decades, clinical studies showed that the brains of people who were in a vegetative state or coma, meaning very minimal electrical brain activity, still consumed massive amounts of energy, Ryan told Live Science. So neuroscientists were faced with a conundrum: If electrical activity isn't using up all the energy in the brain, what is?

Leaky vesicles

In recent years, Ryan and his team have been researching junctions in the brain called synapses, where neurons meet and communicate by launching tiny vesicles packed with chemical messengers called neurotransmitters.

They previously showed that active synapses use up a lot of energy. But in a new study, in which they inactivated rat neuron synapses in lab dishes with a toxin and then measured ATP levels inside the synapses, the team realized that synapses consumed a lot of energy even when neurons weren't firing.

To figure out why, they knocked out various pumps on the surfaces of the tiny vesicles that move neurotransmitters and other molecules in and out, and so deprived synapses of fuel. They imaged the synapses using a fluorescent microscope and figured out how much ATP the synapse had burned. They found that a "proton pump" was responsible for about 44% of all the energy used in the resting synapse. When they dug further, the researchers discovered that the proton pump had to keep working, and burning ATP, because the vesicles were always "leaking" protons.

Inactive synapses prepare to launch these vesicles at a moment's notice by pre-packing them with neurotransmitters.

They do that with the help of another pump that sits on the surfaces of the vesicles. This type of pump, called transporter proteins, change shape to carry neurotransmitters inside and in exchange, they grab a proton from inside the vesicle, change shape again and spit the proton out of the vesicle. For this process to work, the vesicles must have a higher concentration of protons inside than in its surroundings.
But the researchers found that even after the vesicles were full of neurotransmitters, the transporter proteins continued to change shape. Even though they weren't carrying neurotransmitters into the vesicles, they continued to spit protons out, requiring the proton pump to keep working to refill the vesicle's reservoir of protons.

"So we discovered what is sort of an inefficiency in it," Ryan said. The leakage is small, but if you add up trillions of leakages together, that "ends up being quite a large expense even without any electrical activity."

The studies were conducted using rat neurons in the lab, but "the machinery involved is incredibly well conserved" between rats and humans, so the findings would very likely hold true for human brains as well, Ryan said.

It's not clear why our brains evolved to have this leakage, but the easy shape change is likely a trade-off for vesicles to quickly be able to pack neurotransmitters, he said.

Just imagine how quickly you can accelerate if you had a car idling at all times at a high rev rate, but how much fuel you'd waste, he added. "Maybe the price of keeping synapses at the ready was what seems to be an inefficient use of energy."

Ryan and his team hope that the findings may help not only in the fundamental understanding of the human brain, but also clinically. For example, the discovery could lead to a better understanding and treatment of certain diseases, such as Parkinson's, in which the brain may not have enough fuel to make ATP.
In that case, "you're talking about a car idling [and] you cut the gas line," Ryan said. You're "really going to have a problem."

Originally published on Live Science.

Things You Didn't Know About the Brain

Throughout history, the human brain has been remarkably good at dismissing itself. Everyone from ancient Egyptians to Aristotle has downplayed the role of the mysterious stuff between our ears. Famed anatomist Galen gave the brain credit as commander of movement and speech, but even he brushed aside the white and gray matter, figuring the fluid-filled ventricles inside the brain did most of the work.

Human brains are big...

The average adult brain weighs just under 3 pounds (between 1.3 and 1.4 kilograms). Some neurosurgeons describe the texture of a living brain as that of toothpaste, but according to neurosurgeon Katrina Firlik, a better analogy can be found in the local health-food store.

"[The brain] doesn't spread like toothpaste. It doesn't adhere to your fingers the way toothpaste does," Firlik writes in her memoir, "Another Day in the Frontal Lobe: A Brain Surgeon Exposes Life on the Inside" (Random House, 2006). "Tofu — the soft variety, if you know tofu — may be a more accurate comparison."

If you aren't charmed by that description, consider this: About 80 percent of the contents of your cranium is brain, while equal amounts of blood and cerebrospinal fluid, the clear liquid that buffers neural tissue, make up the rest. If you were to blend up all of that brain, blood and fluid, it would come to about 1.7 liters, or not quite enough to fill a 2-liter soda bottle.

...But they're getting smaller

Don't get too cocky about your soda-bottle-sized brain. Humans 5,000 years ago had brains that were even larger.

"We do know from archaeological data that pretty much everywhere we can measure — Europe, China, South Africa, Australia — that brains have

shrunk about 9 cubic inches (150 cubic centimeters), from an average of about 82 in^3 (1,350 cm^3). That's roughly 10 percent," University of Wisconsin at Madison paleoanthropologist John Hawks told LiveScience in 2009.
Researchers don't know why brains might be shrinking, but some theorize that they're evolving to be more efficient. Others think our skulls are getting smaller because our diets include more easily chewable foods and so large, strong jaws are no longer required.

Whatever the reason, brain size doesn't directly correlate with intellect, so there's no evidence that ancient man was brainier than humans of today.

Our brains burn through energy

The modern brain is an energy hog. The organ accounts for about 2 percent of body weight, but it uses about 20 percent of the oxygen in our blood and 25 percent of the glucose (sugars) circulating in our bloodstream, according to the American College of Neuropsychopharmacology.

These energy requirements have spurred a debate among anthropologists about what fueled the evolution of big brains in the first place. Many researchers credit meat, citing evidence of hunting in our early ancestors. But meat would have been an unreliable food source, say other scientists. A 2007 study published in the Proceedings of the National Academy of Science found that modern-day chimps know how to dig for calorie-rich tubers on the savanna. Perhaps our ancestors did the same, boosting their brainpower with veggies.
As for what motivated the brain to balloon in size, there are three major hypotheses: climate change, the demands of ecology, and social competition.

Wrinkles make us smart

What's the secret to our species' smarts? The answer may be wrinkles. The surface of the human brain is convoluted by deep fissures, smaller grooves called sulci, and ridges called gyri. This surface is called the cerebral cortex and is home to about 100 billion neurons, or nerve cells.

The folded, meandering surface allows the brain to pack in more surface area — and thus, more processing power — into the limited confines of the skull. Our primate relatives show varying degrees of convolution in their brains, as do other intelligent creatures like elephants. In fact, research done by Emory University neuroscientist Lori Marino has found that dolphins have even more pronounced brain wrinkles than humans.

Most of our brain cells aren't neurons

The old saw that we use just 10 percent of our brainpower isn't true, but we now know that neurons make up just 10 percent of our brain cells.

The other 90 percent, which account for about half the brain's weight, are called glia, which means "glue" in Greek. Neuroscientists used to think glia were simply the sticky stuff that holds neurons together. But recent research has shown glia to be much more. A 2005 paper in the journal Current Opinions in Neurobiology laid out the roles of these unsung cells, which range from mopping up excess neurotransmitters to providing immune protection to actually promoting and modulating synapse growth and function. (Synapses are the connections between neurons.) It turns out the silent majority isn't so silent after all.

The brain is an exclusive club

Like bouncers at a night club, an assembly of cells in the brain's blood system, called the blood-brain barrier, lets only a few molecules into the nervous system's inner sanctum – the brain. The capillaries that

feed the brain are lined with tightly bound cells, which keep out large molecules. Special proteins in the barrier transport necessary nutrients and substances into the brain. Only an elite few make it through.

The blood-brain barrier protects the brain, but it can also keep out lifesaving medications. Physicians trying to treat brain tumors can use drugs to open the junctions between cells, but that leaves the brain temporarily vulnerable to infection. One new way to sneak meds past the barrier might be nanotechnology. A 2009 study published in the journal Cancer Research showed that specially-engineered nanoparticles can cross the barrier and attach to tumor tissue. In the future, combining nanoparticles with chemotherapy drugs could be one way to target tumors.

The brain starts as a tube

The foundation for the brain is set early. Three weeks after conception, a sheet of embryonic cells called the neural plate folds and fuses into the neural tube. This tissue will become the central nervous system.

The neural tube grows and differentiates throughout the first trimester. (When cells differentiate they specialize into various tissues needed to create body parts.) It isn't until the second trimester that glia and neurons begin to form. The brain doesn't wrinkle up until even later. At 24 weeks, magnetic resonance imaging shows just a few nascent grooves in the otherwise smooth surface of the fetal brain, according to a 2000 study in the journal Radiology. As the third trimester begins in week 26, the grooves deepen and the brain begins to look more like that of a newborn.

Teen brains aren't fully formed

Parents of stubborn teenagers rejoice, or at least relax: That adolescent attitude stems, in part, from the vagaries of brain development.
The gray matter of the brain peaks just before puberty and is pruned back down throughout adolescence, with some of the most dramatic

development happening in the frontal lobes, the seat of judgment and decision-making.

A 2005 study published in the journal Child Development found that the parts of the brain responsible for multitasking don't fully mature until we're 16 or 17 years old. And research presented at the BA Festival of Science in 2006 revealed that teens also have a neural excuse for self-centeredness. When considering an action that would affect others, teens were less likely than adults to use the medial prefrontal cortex, an area associated with empathy and guilt. Teens learn empathy by practicing socializing, the researchers said. So much for grounding them until they're 20.

Brains never stop changing

Scientific wisdom once held that once you hit adulthood, your brain lost all ability to form new neural connections. This ability, called plasticity, was thought to be confined to infancy and childhood.

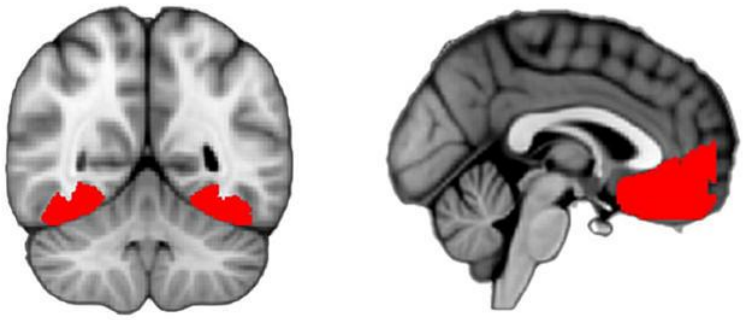
Wrong. A 2007 study on a stroke patient found that her brain had adapted to the damage to nerves carrying visual information by pulling similar information from other nerves. This followed several studies showing that adult mice could form new neurons. Later studies found more evidence of human neurons making new connections into adulthood; meanwhile, research on meditation showed that intense mental training can change both the structure and function of the brain.

Women aren't from Venus after all

Popular culture tells us that women and men's brains are just different. It's true that male and female hormones affect brain development differently, and imaging studies have found brain differences in the ways women and men feel pain, make social decisions and cope with stress. The extent to which these differences are genetic versus shaped by experience — the old nature-versus-nurture debate — is unknown.

But for the most part, male and female brains (and brainpower) are similar. A 2005 American Psychologist analysis of research on gender differences found that in 78 percent of gender differences reported in other studies, the effect of gender on the behavior was in the small or close-to-zero range. And recent studies have debunked myths about the genders' divergent abilities. A study published in the January 2010 Psychological Bulletin looked at almost half a million boys and girls from 69 countries and found no overall gap in math ability. Focusing on our differences may make for catchy book titles, but in neuroscience, nothing is ever that simple.

Brain-imaging study reveals curiosity as it emerges



Human brain-scan images show regions toward the back and front that are active for a person who is feeling curious. Credit: Gottlieb Lab/Columbia's Zuckerman Institute© Provided by Medical Xpress

You look up into the clear blue sky and see something you can't quite identify. Is it a balloon? A plane? A UFO? You're curious, right? A research team based at Columbia's Zuckerman Institute has for the first time witnessed what is happening in the human brain when feelings of curiosity like this arise.

In a study published in the *Journal of Neuroscience*, the scientists revealed brain areas that appear to assess the degree of uncertainty in visually ambiguous situations, giving rise to subjective feelings of curiosity.

"Curiosity has deep biological origins," said corresponding author Jacqueline Gottlieb, Ph.D., a principal investigator at the Zuckerman Institute. The primary evolutionary benefit of curiosity, she added, is to encourage living things to explore their world in ways that help them survive.

"What distinguishes human curiosity is that it drives us to explore much more broadly than other animals, and often just because we want to find things out, not because we are seeking a material reward or survival benefit," said Dr. Gottlieb, who is also a professor of neuroscience at Columbia's Vagelos College of Physicians and Surgeons. "This leads to a lot of our creativity."

Joining Dr. Gottlieb on the research were Michael Cohanpour, Ph.D., a former graduate student at Columbia (now a data scientist with dsm-firmenich), and Mariam Aly, Ph.D., also previously at Columbia and now an acting associate professor of psychology at the University of California, Berkeley.

In the study, researchers employed a noninvasive, widely used technology to measure changes in the blood-oxygen levels in the brains of 32 volunteers. Called functional magnetic resonance imaging, or fMRI, the technology enabled the scientists to record how much oxygen different parts of the subjects' brains consumed as they viewed images. The more oxygen a brain region consumes, the more active it is.

To unveil those brain areas involved in curiosity, the research team presented participants with special images known as texforms. These are images of objects, such as a walrus, frog, tank or hat, that have been distorted to various degrees to make them more or less difficult to recognize.

The researchers asked participants to rate their confidence and curiosity about each texform, and found that the two ratings were inversely related. The more confident subjects were that they knew what the texform depicts, the less curious they were about it. Conversely, the less confident subjects were that they could guess what the texform was, the more curious they were about it.

Using fMRI, the researchers then viewed what was happening in the brain as the subjects were presented with texforms. The brain-scan data showed high activity in the occipitotemporal cortex (OTC), a region located just above your ears, which has long been known to be involved in vision and in recognizing categories of objects.

Based on previous studies, the researchers expected that when they presented participants with clear images, this brain region would show distinct activity patterns for animate and inanimate objects. "You can think of each pattern as a 'barcode' identifying the texform category," Dr. Gottlied said.

The researchers used these patterns to develop a measure, which they dubbed "OTC uncertainty," of how uncertain this cortical area was about the category of a distorted texform. They showed that, when subjects were less curious about a texform, their OTC activity corresponded to only one barcode, as if it clearly identified whether the image belonged to the animate or the inanimate category. In contrast, when subjects were more curious, their OTC had characteristics of both barcodes, as if it could not clearly identify the image category.

Also active during the texform presentations were two regions in the front of the brain. One is the anterior cingulate cortex, which previous studies implicated in information gathering. The other is the ventromedial prefrontal cortex (vmPFC), which is involved in monitoring a person's subjective perceptions of value and confidence about different situations. In the new study, both areas were more active when subjects reported being more confident in knowing a texform's identity (and thus, less curious to see the clarified image).

Importantly, said Dr. Gottlieb, vmPFC activity seemed to provide a neurological bridge between the subjective feeling of curiosity and the OTC certainty measure. It's as though this region read out the uncertainty encoded by the distributed activity pattern in the OTC and helped a person decide if they needed to be curious about the texform.

"This is really the first time we can link the subjective feeling of curiosity about information to the way your brain represents that information," Dr. Gottlieb said.

The study has two important implications, Dr. Gottlieb said. First, although the study focused on perceptual curiosity elicited by visual stimuli, people experience other forms of curiosity, such as curiosity about trivia questions and factual

matters (i.e. how tall is the Eiffel tower?) or social curiosity (which restaurant did my friends go to last night?).

One intriguing possibility of the study, she noted, is that the mechanism it has uncovered may generalize to other forms of curiosity. For example, an fMRI study investigating sounds of varying recognizability may show that auditory areas in the brain convey the uncertainty regarding the sound and the vmPFC reads out this uncertainty to determine curiosity.

A second possibility on Dr. Gottlieb's mind is that the findings could have diagnostic and even therapeutic implications for those with depression, apathy or anhedonia (the inability to feel pleasure), which are conditions often marked by a lack of curiosity.

"Curiosity entails a sort of enthusiasm, a willingness to expend energy and investigate your surroundings. And it's intrinsically motivated, meaning that nobody is paying you to be curious; you are curious merely based on the hope that something good will come when you learn," Dr. Gottlieb said. "Those are just some of the amazing things about curiosity."

More information: Michael Cohanpour et al, Neural Representations of Sensory Uncertainty and Confidence are Associated with Perceptual Curiosity, *The Journal of Neuroscience* (2024). DOI: 10.1523/JNEUROSCI.0974-23.2024

Provided by Columbia University

Neurons in The Brain Appear to Follow a Distinct Mathematical Pattern

Researchers taking part in the Human Brain Project have identified a mathematical rule that governs the distribution of neurons in our brains.

The rule predicts how neurons are distributed in different parts of the brain, and could help scientists create precise models to understand how the brain works and develop new treatments for neurological diseases.

In the wonderful world of statistics, if you consider any continuous random variable, the logarithm of that variable will often follow what's known as a lognormal distribution. Defined by the mean and standard deviation, it can be visualized as a bell-shaped curve, only with the curve being wider than what you'd find in a normal distribution.

A team of researchers from the Jülich Research Center and the University of Cologne in Germany found the number of neurons in areas of the outer layer of neural tissue in different mammals fits a lognormal distribution.

Mathematics aside, a simple and important distinction is the symmetry of the normal distribution bell curve and the asymmetry and heavy right-skewed tail of the lognormal distribution, due to a large number of small values and a few significantly large values.

The size of a population across a country is often lognormally distributed, with a few very large cities and many small towns and villages.

Brain structure and function depend on neuron numbers and arrangement. The density of neurons in different regions and layers of that outer tissue layer – the cerebral cortex – varies considerably.

"The distribution of neuron densities influences the network connectivity," says neuroscientist Sacha van Albada of the Jülich Research Center.

"For instance, if the density of synapses is constant, regions with lower neuron density will receive more synapses per neuron."

The statistical distributions of neuron densities are still largely unknown, though research has certainly provided us with fascinating discoveries about our brain's cellular tissues.

To conduct their research, the team used nine open-source datasets covering seven different species: mouse, marmoset, macaque, galago, owl monkey, baboon, and human. When the neuron densities in different regions of the cortex were compared, a common pattern of a lognormal distribution emerged.

"Our results are in agreement with the observation that surprisingly many characteristics of the brain follow lognormal distributions," the authors write in their paper.

A lognormal distribution is a natural result of processes that multiply, just like normal distribution is a natural result of adding up many independent variables.

"One reason why it may be very common in nature is because it emerges when taking the product of many independent variables," says Alexander van Meegen, who co-led the research as part of his PhD in computational neuroscience at the Jülich Research Centre.

The researchers say the way the cortex is structured could be a byproduct of development or evolution that has nothing to do with computation.

But previous research suggests brain neural network variation is more than just a byproduct and may actively help animals learn in changing environments. And the fact that the same organization can be seen in different species and in most parts of the cortex suggests that the lognormal distribution is used for something.

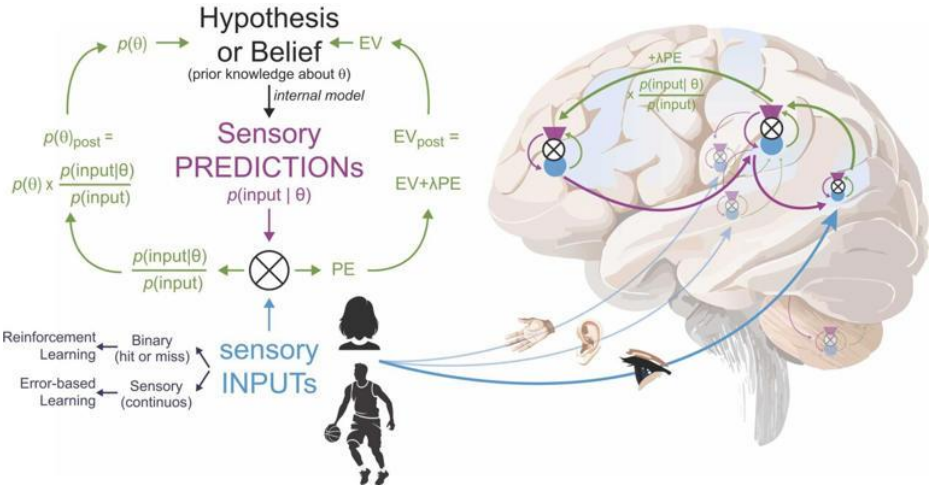
"We cannot be sure how the lognormal distribution of neuron densities will influence brain function, but it will likely be associated with high network heterogeneity, which may be computationally beneficial," explains co-lead author Aitor Morales-Gregorio, a computational neuroscientist at the Jülich Research Centre.

Scientists hope this discovery will shed light on how the brain stores and retrieves information, as well as how it acquires new knowledge. In the ongoing quest to find effective treatments for brain disease, it may pave the way for the creation of new drugs that target specific regions of the brain.

The Human Brain Project's ten-year effort to establish a shared research infrastructure for boosting neuroscience, computing, and brain-related medicine is coming to a close, and it's given us some interesting discoveries along the way.

The study has been published in *Cerebral Cortex*.

How the brain plans ahead to predict the world



How predictive coding, Bayesian inference and learning processes come together. Credit: Neuroscience & Biobehavioral Reviews (2024). DOI: 10.1016/j.neubiorev.2024.105877

Your brain not only processes what you see but continuously makes predictions based on your experiences. This process may be less finetuned in people with autism.

When someone throws a ball at you, you almost immediately know to catch it—even before you consciously realize it. In the past, people thought that in such a situation, the brain functioned like a camera: an image of the flying ball enters through your eyes and is then processed by your brain. The brain then programs an appropriate action to react to it. But doesn't that process take too long? Would you still be able to catch the ball in time?

Researchers Christian Keysers, Giorgia Silani, and Valeria Gazzola show that this process in the brain works differently. Christian explains, "Your brain doesn't react to what enters the eye—but it predicts what will happen, based on expectations and previous experiences. By doing so, our actions keep pace with the ball, despite the hundreds of milliseconds it takes the brain to process visual input and move our body.

"It plans ahead to allow time to execute the action and catch the ball. The image that enters through your eyes is mainly used to check if your expectations match reality. Only when there's a difference between your expectations and what you see, does your brain use the visual input to nudge its expectations in a more accurate direction."

The research is published in the journal *Neuroscience & Biobehavioral Reviews*.

Predicting others

Gazzola says, "What's interesting is that you also use your own motor programs and somatosensory cortices to predict the actions of others. When you perform a physical action, like lifting a carton of milk to pour some of it into your coffee, you have expectations about the weight of the carton, and how it should feel in your hand when you start lifting it.

"You don't really notice the weight of the carton consciously, because your brain predicted it. But if someone else has already finished the milk, and the carton is so much lighter than you expected, the sudden difference between your expectations and the sensory feedback suddenly grabs your attention.

"When you see someone else do so, you don't directly feel the weight of the carton. Still, you can make predictions using your own motor programs, and test them against what you see. So, you still feel surprised if the carton flies skywards much faster than you expected.

"We think this has to do with so-called mirror neurons, which are cells within your own motor cortex that become active when you see someone else perform an action. This acts as a sort of 'shortcut,' allowing you to use your own motor programs, and the predictive machinery necessary for your own actions to predict the behavior of others."

But what about emotions? Gazzola explains, "We know that regions in our brain that are involved in our own emotions become active while we witness the emotions of others. However, how we predict the emotions of others is not fully understood. Reviewing the literature revealed that the regions in our brain that are active when we receive reward or punishment also become active when

someone else receives reward or punishment. Reward and punishment are therefore valuable predictors for the emotions of others."

Complex system

Keysers says, "Imagine I have a button, and every time I press it, an actor starts screaming in pain. If I do this five times, your expectations change: the first time, it's totally unexpected, but by the fifth time, you can predict what will happen.

"According to the traditional theory of perception, where the brain only processes the image you see, you should see the same reaction in the brain each time. But if the outside world primarily serves to test your predictions, you'd expect a strong brain response the first time, and a much smaller response the last time, because you already know what's going to happen.

"So what actually happens in the brain? Over many studies, we see that it's quite complex. Some brain areas respond relatively consistently across all five times. At the same time, there are also brain regions where activity changes across the five times. In this review paper, we look at the many studies that have emerged on the topic to propose how these different brain systems organize into a coherent predictive brain.

"For example, if some actions become predictable, your premotor cortex knows how to perform the action in your body. This region will then inhibit visual regions in your brain, leading to less visual input. What you perceive is then no longer what you actually see, but what you expect to see. Only if something unexpected happens, does this inhibition become ineffective. The visual areas now show a strong response that is sent forwards to the premotor cortex to revise the predictions."

Predictions and autism

It's believed that the predictive system in people with autism is less well-tuned. This makes the world around them more unpredictable, leading to less suppressed stimuli.

Keysers explains, "Imagine you're standing in a crowded room with many people. Because our brain makes a lot of predictions, we can ignore most stimuli and

focus only on what's important. But when this predictive system doesn't work well, such a busy environment can suddenly feel overwhelming.

"The brain is complex and has the unique ability to adapt. It's interesting to realize that your brain isn't just a camera simply processing what comes in. Instead, your brain constantly operates based on predictions. Your brain is always ahead and continuously constructs what the world should be."

More information: Christian Keysers et al, Predictive coding for the actions and emotions of others and its deficits in autism spectrum disorders, *Neuroscience & Biobehavioral Reviews* (2024). DOI: 10.1016/j.neubiorev.2024.105877

Provided by Netherlands Institute for Neuroscience - KNAW