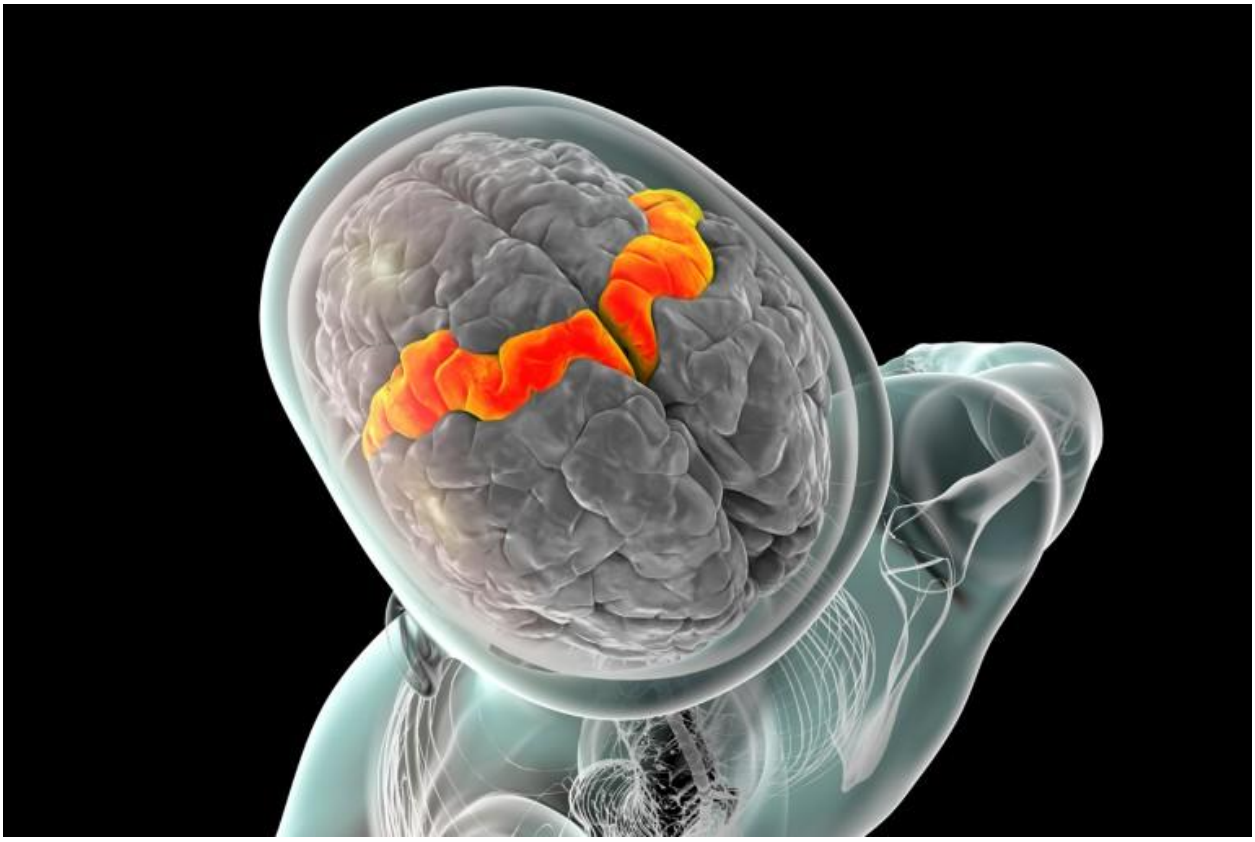
BRAIN INTRACRANIAL VOL 10

World first: brain implant lets man speak with expression — and sing 13 June 2025

Device translates thought to speech in real time.



The motor cortex (orange, illustration). Electrodes implanted in this region helped to record the speech-related brain activity of a man who could not speak intelligibly. Credit: Kateryna Kon/Science Photo Library

A man with a severe speech disability is able to speak expressively and sing using a brain implant that translates his neural activity into words almost instantly. The device conveys changes of intonation when he asks questions, emphasizes the words of his choice and allows him to hum a string of notes in three pitches.

The system — known as a brain–computer interface (BCI) — used artificial intelligence (AI) to decode the participant's electrical brain activity as he attempted to speak. The device is the first to reproduce not only a person's intended words but also features of natural speech such as intonation, pitch and emphasis, which help to express meaning and emotion.

In a study, a synthetic voice that mimicked the participant's own spoke his words within 10 milliseconds of the neural activity that signalled his intention to speak. The system, described today in *Nature*[1], marks a significant improvement over earlier BCI models, which streamed speech within three seconds or produced it only after users finished miming an entire sentence.

"This is the holy grail in speech BCIs," says Christian Herff, a computational neuroscientist at Maastricht University, the Netherlands, who was not involved in the study. "This is now real, spontaneous, continuous speech."

Real-time decoder

The study participant, a 45-year-old man, lost his ability to speak clearly after developing amyotrophic lateral sclerosis, a form of motor neuron disease, which damages the nerves that control muscle movements, including those needed for speech. Although he could still make sounds and mouth words, his speech was slow and unclear.

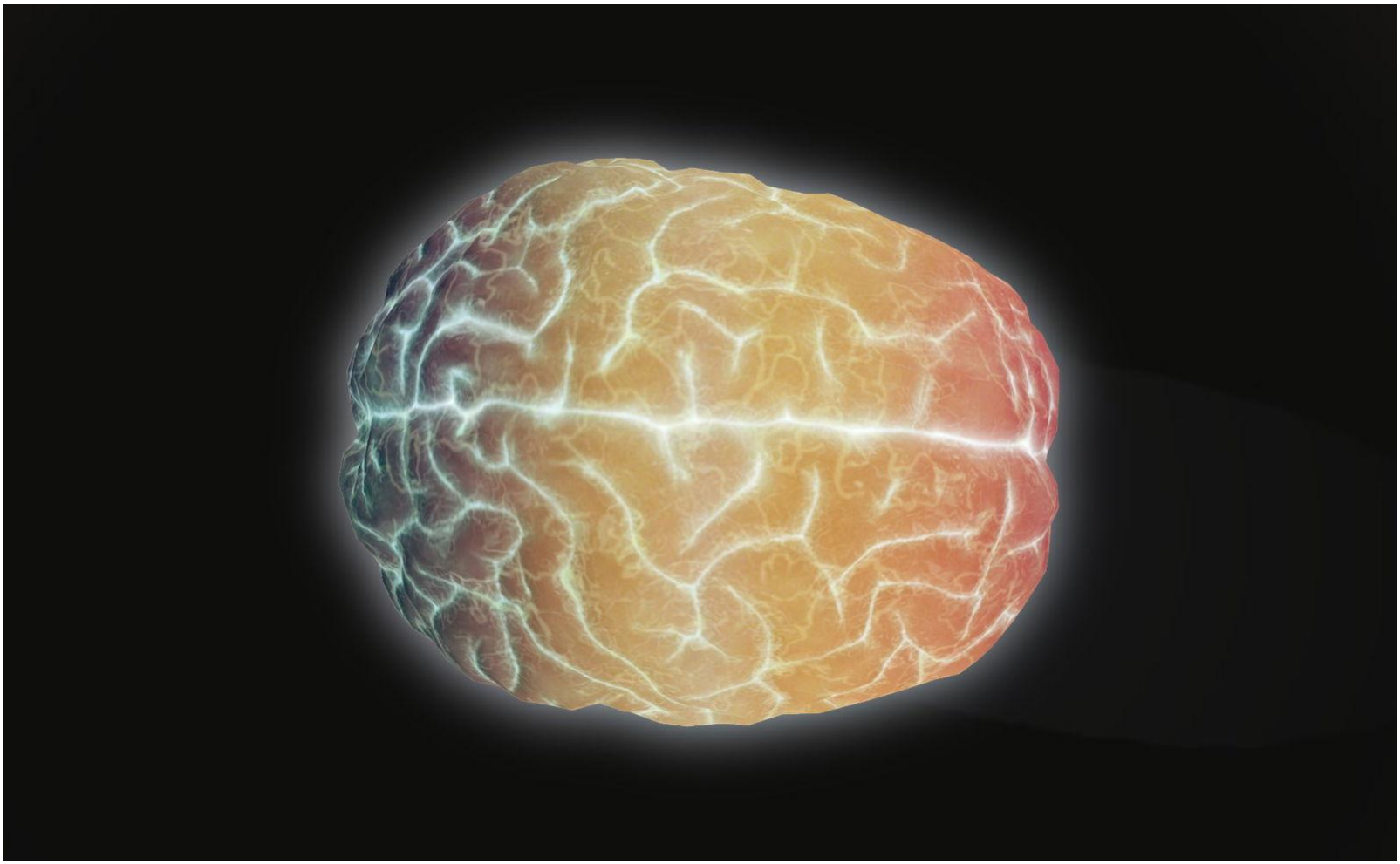
Mind-reading devices are revealing the brain's secrets

Five years after his symptoms began, the participant underwent surgery to insert 256 silicon electrodes, each 1.5-mm long, in a brain region that controls movement. Study co-author

Maitreyee Wairagkar, a neuroscientist at the University of California, Davis, and her colleagues trained deep-learning algorithms to capture the signals in his brain every 10 milliseconds. Their system decodes, in real time, the sounds the man attempts to produce rather than his intended words or the constituent phonemes — the subunits of speech that form spoken words.

“We don’t always use words to communicate what we want. We have interjections. We have other expressive vocalizations that are not in the vocabulary,” explains Wairagkar. “In order to do that, we have adopted this approach, which is completely unrestricted.”

The team also personalized the synthetic voice to sound like the man’s own, by training AI algorithms on recordings of interviews he had done before the onset of his disease.



SCIENTISTS DETECT LIGHT PASSING THROUGH A HUMAN HEAD IN MEDICAL FIRST

MJ BANIAS·JUNE 17, 2025

Physicists have demonstrated the first successful detection of light transmitted through an entire adult human skull, overcoming attenuation levels previously considered impossible.

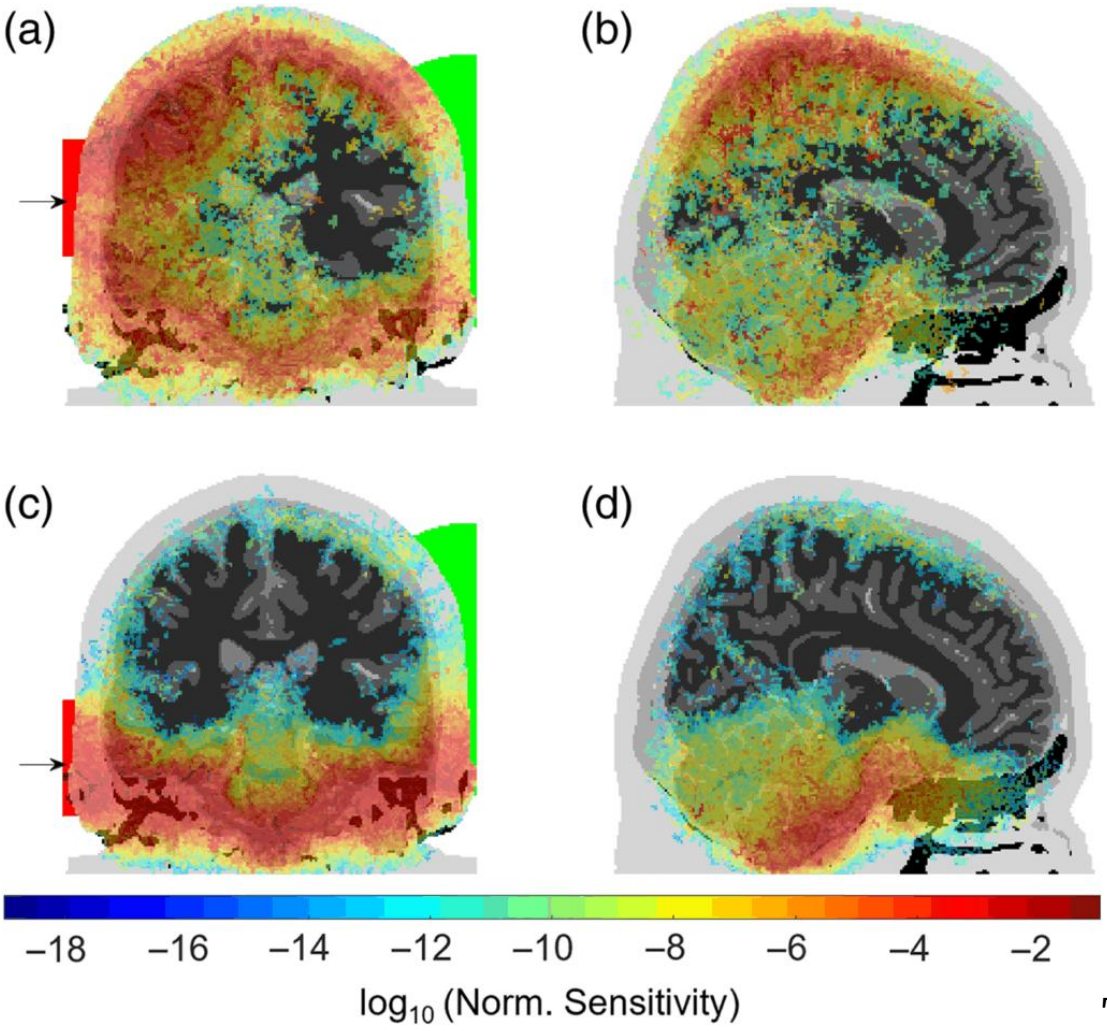
Published in *Neurophotonics*, the study reveals how carefully engineered laser systems and single-photon detection methods enabled researchers to track photons traveling 15.5 cm across a human head—a feat with profound implications for non-invasive brain scan technology.

The team used a special pulsed laser and a time-correlated single-photon counting system to detect photons surviving a journey through skin, skull, cerebrospinal fluid, and brain matter. Despite attenuation equivalent to just one photon surviving per quintillion emitted, the system recorded approximately one photon per second after 30 minutes of data collection.

So what exactly does this all look like?

In a setup that could double as the world's most precise game of laser tag, researchers fired pulses of light at one side of a participant's head while an ultra-sensitive detector waited opposite, ready to catch photons that survived the journey. Blocking all other light in the room, the researchers then waited to see if the detector began to pick up any photons.

Previous computer simulations indicated that light would take certain routes through the brain in order to make it out the other side, and the experimental results came incredibly close. While photons did manage to make it through the dense and complex brain material, and exit the other side, they generally preferred to travel via the cerebrospinal fluid (which is the clear protective fluid that surrounds the brain and spinal cord).



The sensitivity map for the source position approximately matching the experimental conditions [(a) and (b)] and 40 mm lower than experimental conditions [(c) and (d)]. The detector area is the intersection of a sphere (green) and the surface of the head. (Image: Radford, et al. SPIE)Clinically, the technology could revolutionize access to deep-brain diagnostics. Current optical methods for brain scans like functional near-infrared spectroscopy (fNIRS) penetrate only 4 cm, limiting monitoring to the surface of the brain. By contrast, the transmitted photons in this study carried information from sulci (brain folds), midbrain nuclei, and cerebellar regions which are critical areas for understanding neurological disorders. The authors suggest portable versions could detect subcortical hemorrhages or tumors in resource-limited settings where MRI remains unavailable.

However, significant barriers remain.

Successful detection occurred only in a fair-skinned, hairless participant among eight test subjects, highlighting biological variability in optical properties. The 30-minute acquisition time and reliance on 1.2 W lasers, which are near the safety limits for skin exposure, also pose practical challenges. Suffice it to say, while blasting someone's head with a laser worked, it needs some fine tuning to become viable for medical bedside use.

That being said, this research establishes a framework for developing optical systems that combine the portability of EEG with the depth resolution of fMRI, which could be a significant boon for global healthcare accessibility. As computational methods and detector technologies advance, the dream of affordable, non-invasive deep-brain imaging appears increasingly within reach.

Thinking in sync: How brain rhythms support intelligence

Researchers at Johannes Gutenberg University Mainz discover midfrontal theta wave synchronisation enhances cognitive flexibility and focus.

From Johannes Gutenberg Universitaet Mainz 17/06/25 (first released 16/06/25)

Test subject in an EEG booth Credit: photo/©: Henrike Jungeblut / Luis Ahrens

When the brain is under pressure, certain neural signals begin to move in sync – much like a well-rehearsed orchestra.

A new study from Johannes Gutenberg University Mainz (JGU) is the first to show how flexibly this neural synchrony adjusts to different situations and that this dynamic coordination is closely linked to cognitive abilities.

"Specific signals in the midfrontal brain region are better synchronized in people with higher cognitive ability – especially during demanding phases of reasoning," explained Professor Anna-Lena Schubert from JGU's Institute of Psychology, lead author of the study recently published in the *Journal of Experimental Psychology: General.*

The researchers focused on the midfrontal area of the brain and the measurable coordination of the so-called theta waves.

These brainwaves oscillate between four and eight hertz and belong to the group of slower neural frequencies.

“They tend to appear when the brain is particularly challenged such as during focused thinking or when we need to consciously control our behavior,” said Schubert, who heads the Analysis and Modeling of Complex Data Lab at JGU.

Being able to focus even next to a buzzing phone

The 148 participants in the study, aged between 18 and 60, first completed tests assessing memory and intelligence before their brain activity was recorded using electroencephalography (EEG).

This method measures tiny electrical signals in the brain using electrodes placed on the scalp and is a well-established technique for gaining precise insights into cognitive processes.

During EEG recording, participants completed three mentally demanding tasks designed to assess cognitive control.

The researchers were interested in the participants’ ability to flexibly shift between changing rules, which is an essential aspect of intelligent information processing.

For example, participants had to press a button to decide whether a number was even or odd, and moments later whether it was greater or less than five.

Each switch of rules required rapid adjustment of mental strategies – a process that allowed researchers to closely observe how the brain’s networks coordinate in real time.

As a result, individuals with higher cognitive abilities showed especially strong synchronization of theta waves during crucial moments, particularly when making decisions.

Their brains were better at sustaining purposeful thought when it mattered most.

“People with stronger midfrontal theta connectivity are often better at maintaining focus and tuning out distractions, be it that your phone buzzes while you’re working or that you intend to read a book in a busy train station,” explained Schubert.

A flexible rhythm in the brain

Professor Anna-Lena Schubert was particularly surprised by how closely this brain rhythm coordination was tied to cognitive abilities.

“We did not expect the relationship to be this clear,” she said.

What mattered most was not continuous synchronization, but the brain’s ability to adapt its timing flexibly and contextually – like an orchestra that follows a skilled conductor.

The midfrontal region often sets the tone in this coordination but works in concert with other areas across the brain.

This midfrontal theta connectivity appears to be particularly relevant during the execution of decisions, however not during the preparatory mental adjustment to new task rules.

Previous EEG studies on cognitive ability mostly examined activity in isolated brain regions.

In contrast, this study took a network-level approach, examining how different areas interact across multiple tasks to identify stable, overarching patterns.

The findings show that individual differences in cognitive ability are linked to the brain's dynamic network behavior.

"Potential applications such as brain-based training tools or diagnostics are still a long way off," emphasized Schubert.

"But our study offers important groundwork for understanding how intelligence functions at a neural level."

A follow-up study, now seeking participants aged 40 and older from the Rhine-Main region, will explore which biological and cognitive factors further support this kind of efficient brain coordination and the role of additional cognitive abilities, such as processing speed and working memory.

Paper

Trait characteristics of midfrontal theta connectivity as a neurocognitive measure of cognitive control and its relation to general cognitive abilities.

Schubert, A.-L., Löffler, C., Jungeblut, H. M., & Hülsemann, M. J. (2025). Trait characteristics of midfrontal theta connectivity as a neurocognitive measure of cognitive control and its relation to general cognitive abilities. *Journal of Experimental Psychology: General.* Advance online publication. https://doi.org/10.1037/xge0001780
Understanding the neurocognitive basis of cognitive control and its relationship with general cognitive ability is a key challenge in individual differences research. This study investigates midfrontal theta connectivity as a neurocognitive marker for individual differences in cognitive control. Using electroencephalography, we examined midfrontal global theta connectivity across three distinct cognitive control tasks in 148 participants. Our findings reveal that midfrontal theta connectivity can be modeled as a trait-like latent variable, indicating its consistency across tasks and stability over time. However, the reliability of the observed measures was found to be low to moderate, suggesting substantial measurement error. We also replicated previous results, finding a strong correlation (r = 0.64) between midfrontal theta connectivity and cognitive abilities,

especially during higher order stages of information processing. We disentangled the specific cognitive processes contributing to this relationship by employing a task-cueing paradigm with distinct cue and target intervals. The results indicated that only theta connectivity during response-related processes, not during cue-evoked task-set reconfiguration, correlated with cognitive abilities. These insights significantly advance theoretical models of intelligence, highlighting the critical role of specific aspects of cognitive control in cognitive abilities. (PsycInfo Database Record (c) 2025 APA, all rights reserved)

Impact Statement

We show that midfrontal theta connectivity, measured through electroencephalography, can serve as a marker for general cognitive ability. We found that individuals with higher cognitive ability exhibit stronger midfrontal theta connectivity during response-related processes in cognitive control tasks. These findings advance our understanding of how brain network dynamics contribute to cognitive abilities. This research underscores the importance of neural connectivity in cognitive performance, offering insights that could inform cognitive training programs or brain stimulation research. (PsycInfo Database Record (c) 2025 APA, all rights reserved)

What the human brain can do that AI can’t

University of Amsterdam researchers reveal unique brain activations, showing AI’s limitations in understanding action opportunities.

From Universiteit van Amsterdam 17/06/25 (first released 16/06/25)

Illustration by Superinnovators

How do you intuitively know that you can walk on a footpath and swim in a lake?

Researchers from the University of Amsterdam have discovered unique brain activations that reflect how we can move our bodies through an environment.

The study not only sheds new light on how the human brain works, but also shows where artificial intelligence is lagging behind.

According to the researchers, AI could become more sustainable and human-friendly if it incorporated this knowledge about the human brain.

When we see a picture of an unfamiliar environment – a mountain path, a busy street, or a river – we immediately know how we could move around in it: walk, cycle, swim or not go any further.

That sounds simple, but how does your brain actually determine these action opportunities?

PhD student Clemens Bartnik and a team of co-authors show how we make estimates of possible actions thanks to unique brain patterns.

The team, led by computational neuroscientist Iris Groen, also compared this human ability with a large number of AI models, including ChatGPT. ‘AI models turned out to be less good at this and still have a lot to learn from the efficient human brain,’ Groen concludes.

Viewing images in the MRI scanner

Using an MRI scanner, the team investigated what happens in the brain when people look at various photos of indoor and outdoor environments.

The participants used a button to indicate whether the image invited them to walk, cycle, drive, swim, boat or climb.

At the same time, their brain activity was measured.

‘We wanted to know: when you look at a scene, do you mainly see what is there – such as objects or colours – or do you also automatically see what you can do with it,’ says Groen. ‘Psychologists call the latter “affordances” – opportunities for action; imagine a staircase that you can climb, or an open field that you can run through.’

Unique processes in the brain

The team discovered that certain areas in the visual cortex become active in a way that cannot be explained by visible objects in the image.

‘What we saw was unique,’ says Groen.

‘These brain areas not only represent what can be seen, but also what you can do with it.’

The brain did this even when participants were not given an explicit action instruction.

‘These action possibilities are therefore processed automatically,’ says Groen.

‘Even if you do not consciously think about what you can do in an environment, your brain still registers it.’

The research thus demonstrates for the first time that affordances are not only a psychological concept, but also a measurable property of our brains.

What AI doesn't understand yet

The team also compared how well AI algorithms – such as image recognition models or GPT-4 – can estimate what you can do in a given environment.

They were worse at predicting possible actions. 'When trained specifically for action recognition, they could somewhat approximate human judgments, but the human brain patterns didn't match the models' internal calculations,' Groen explains.

'Even the best AI models don't give exactly the same answers as humans, even though it's such a simple task for us,' Groen says. 'This shows that our way of seeing is deeply intertwined with how we interact with the world.

We connect our perception to our experience in a physical world.

AI models can't do that because they only exist in a computer.'

AI can still learn from the human brain

The research thus touches on larger questions about the development of reliable and efficient AI. 'As more sectors – from healthcare to robotics – use AI, it is becoming important that machines not only recognise what something is, but also understand what it can do,' Groen explains.

'For example, a robot that has to find its way in a disaster area, or a self-driving car that can tell apart a bike path from a driveway.'

Groen also points out the sustainable aspect of AI. 'Current AI training methods use a huge amount of energy and are often only accessible to large tech companies.

More knowledge about how our brain works, and how the human brain processes certain information very quickly and efficiently, can help make AI smarter, more economical and more human-friendly.'

Paper

Representation of locomotive action affordances in human behavior, brains, and deep neural networks

Clemens G. Bartnik, Christina Sartzetaki, Abel Puigseslloses Sanchez, +3, and Iris I. A. Groen Authors Info & Affiliations
Edited by William H. Warren, Brown University, Providence, RI; received July 14, 2024; accepted April 14, 2025 by Editorial Board Member Peter L. Strick
June 12, 2025
122 (24) e2414005122
https://doi.org/10.1073/pnas.2414005122 Vol. 122 | No. 24

To navigate the world around us, we can use different actions, such as walking, swimming, or climbing. How does our brain compute and represent such locomotive action affordances? Here, we show that activation patterns in visual regions in the human brain represent information about affordances independent of other visual elements such as surface materials and objects, and do so in an automatic manner. We also demonstrate that commonly used models of visual processing in human brains, namely object- and scene-classification trained deep neural networks, do not strongly represent this information. Our results suggest that locomotive action affordance perception in scenes relies on specialized neural representations different from those used for other visual understanding tasks.

Abstract

To decide how to move around the world, we must determine which locomotive actions (e.g., walking, swimming, or climbing) are afforded by the immediate visual environment. The neural basis of our ability to recognize locomotive affordances is unknown. Here, we compare human behavioral annotations, functional MRI (fMRI) measurements, and deep neural network (DNN) activations to both indoor and outdoor real-world images to demonstrate that the human visual cortex represents locomotive action affordances in complex visual scenes. Hierarchical clustering of behavioral annotations of six possible locomotive actions show that humans group environments into distinct affordance clusters using at least three separate dimensions. Representational similarity analysis of multivoxel fMRI responses in the scene-selective visual cortex shows that perceived locomotive affordances are represented independently from other scene properties such as objects, surface

materials, scene category, or global properties and independent of the task performed in the scanner. Visual feature activations from DNNs trained on object or scene classification as well as a range of other visual understanding tasks correlate comparatively lower with behavioral and neural representations of locomotive affordances than with object representations. Training DNNs directly on affordance labels or using affordance-centered language embeddings increases alignment with human behavior, but none of the tested models fully captures locomotive action affordance perception. These results uncover a type of representation in the human brain that reflects locomotive action affordances.

How the brain solves complicated problems

Study shows humans flexibly deploy different reasoning strategies to tackle challenging mental tasks — offering insights for building machines that think more like us.

Anne Trafton | MIT News Publication Date: June 11, 2025

The human brain is very good at solving complicated problems. One reason for that is that humans can break problems
apart into manageable subtasks that are easy to solve one at a time.

This allows us to complete a daily task like going out for coffee by breaking it into steps: getting out of our office building, navigating to the coffee shop, and once there, obtaining the coffee. This strategy helps us to handle obstacles easily. For example, if the elevator is broken, we can revise how we get out of the building without changing the other steps.

While there is a great deal of behavioral evidence demonstrating humans' skill at these complicated tasks, it has been difficult to devise experimental scenarios that allow precise characterization of the computational strategies we use to solve problems.

In a new study, MIT researchers have successfully modeled how people deploy different decision-making strategies to solve a complicated task — in this case, predicting how a ball will travel through a maze when the ball is hidden from view. The human brain cannot perform this task perfectly because it is impossible to track all of the possible trajectories in parallel, but the researchers found that people can perform reasonably well by flexibly adopting two strategies known as hierarchical reasoning and counterfactual reasoning.

The researchers were also able to determine the circumstances under which people choose each of those strategies.

"What humans are capable of doing is to break down the maze into subsections, and then solve each step using relatively simple algorithms. Effectively, when we don't have the means to solve a complex problem, we manage by using simpler heuristics that get the job done," says Mehrdad Jazayeri, a professor of brain and cognitive sciences, a member of MIT's McGovern Institute for Brain Research, an investigator at the Howard Hughes Medical Institute, and the senior author of the study.

Mahdi Ramadan PhD '24 and graduate student Cheng Tang are the lead authors of the paper, which appears today in *Nature Human Behavior*. Nicholas Watters PhD '25 is also a co-author.

Rational strategies

When humans perform simple tasks that have a clear correct answer, such as categorizing objects, they perform extremely well. When tasks become more complex, such as planning a trip to your favorite cafe, there may no longer be one clearly superior answer. And, at each step, there are many things that could go wrong. In these cases, humans are very good at working out a solution that will get the task done, even though it may not be the optimal solution.

Those solutions often involve problem-solving shortcuts, or heuristics. Two prominent heuristics humans commonly rely on are hierarchical and counterfactual reasoning. Hierarchical reasoning is the process of breaking down a problem into layers, starting from the general and proceeding toward specifics. Counterfactual reasoning involves imagining what would have happened if you had made a different choice. While these strategies are well-known, scientists don't know much about how the brain decides which one to use in a given situation.

"This is really a big question in cognitive science: How do we problem-solve in a suboptimal way, by coming up with clever heuristics that we chain together in a way that ends up getting us closer and closer until we solve the problem?" Jazayeri says.

To overcome this, Jazayeri and his colleagues devised a task that is just complex enough to require these strategies, yet simple enough that the outcomes and the calculations that go into them can be measured.

The task requires participants to predict the path of a ball as it moves through four possible trajectories in a maze. Once the ball enters the maze, people cannot see which path it travels. At two junctions in the maze, they hear an

auditory cue when the ball reaches that point. Predicting the ball's path is a task that is impossible for humans to solve with perfect accuracy.

"It requires four parallel simulations in your mind, and no human can do that. It's analogous to having four conversations at a time," Jazayeri says. "The task allows us to tap into this set of algorithms that the humans use, because you just can't solve it optimally."

The researchers recruited about 150 human volunteers to participate in the study. Before each subject began the ball-tracking task, the researchers evaluated how accurately they could estimate timespans of several hundred milliseconds, about the length of time it takes the ball to travel along one arm of the maze.

For each participant, the researchers created computational models that could predict the patterns of errors that would be seen for that participant (based on their timing skill) if they were running parallel simulations, using hierarchical reasoning alone, counterfactual reasoning alone, or combinations of the two reasoning strategies.

The researchers compared the subjects' performance with the models' predictions and found that for every subject, their performance was most closely associated with a model that used hierarchical reasoning but sometimes switched to counterfactual reasoning.

That suggests that instead of tracking all the possible paths that the ball could take, people broke up the task. First, they picked the direction (left or right), in which they thought the ball turned at the first junction, and continued to track the ball as it headed for the next turn. If the timing of the next sound

they heard wasn't compatible with the path they had chosen, they would go back and revise their first prediction — but only some of the time.

Switching back to the other side, which represents a shift to counterfactual reasoning, requires people to review their memory of the tones that they heard. However, it turns out that these memories are not always reliable, and the researchers found that people decided whether to go back or not based on how good they believed their memory to be.

"People rely on counterfactuals to the degree that it's helpful," Jazayeri says. "People who take a big performance loss when they do counterfactuals avoid doing them. But if you are someone who's really good at retrieving information from the recent past, you may go back to the other side."

Human limitations

To further validate their results, the researchers created a machine-learning neural network and trained it to complete the task. A machine-learning model trained on this task will track the ball's path accurately and make the correct prediction every time, unless the researchers impose limitations on its performance.

When the researchers added cognitive limitations similar to those faced by humans, they found that the model altered its strategies. When they eliminated the model's ability to follow all possible trajectories, it began to employ hierarchical and counterfactual strategies like humans do. If the researchers reduced the model's memory recall ability, it began to switch to counterfactual only if it thought its recall would be good enough to get the right answer — just as humans do.

“What we found is that networks mimic human behavior when we impose on them those computational constraints that we found in human behavior,” Jazayeri says. “This is really saying that humans are acting rationally under the constraints that they have to function under.”

By slightly varying the amount of memory impairment programmed into the models, the researchers also saw hints that the switching of strategies appears to happen gradually, rather than at a distinct cut-off point. They are now performing further studies to try to determine what is happening in the brain as these shifts in strategy occur.

The research was funded by a Lisa K. Yang ICoN Fellowship, a Friends of the McGovern Institute Student Fellowship, a National Science Foundation Graduate Research Fellowship, the Simons Foundation, the Howard Hughes Medical Institute, and the McGovern In

Autonomic nervous system is key driver of global fMRI signal, study finds

by Ingrid Fadelli, Phys.org edited by Sadie Harley, reviewed by Robert Egan

Global fMRI fluctuations are associated with systemic physiological changes. Credit: *Nature Neuroscience* (2025). DOI: 10.1038/s41593-025-01945-y.
The activity of the human brain is known to be closely connected to other physiological signals, such as heart rate and breathing. A study by researchers at the University of California Los Angeles (UCLA) and other institutes reveals that a global spatiotemporal pattern in the brain (i.e. a pattern in brain activity that repeats itself across the brain and over time) is a central component of these brain-body interactions.

The same research team has now set out to further investigate this global signal, in the hope of identifying its underlying physiological and neural origins. Their findings, published in *Nature Neuroscience*, show that this unified pattern of brain-body activity is in great part driven by the autonomic nervous system, the part of the nervous system regulating arousal and other involuntary bodily functions.

"The inspiration for this project came from our previously published paper in *Nature Neuroscience* where we described prominent spatiotemporal patterns in brain functional magnetic resonance imaging (fMRI) signals," Taylor Bolt, first author of the paper, told Medical Xpress.

"Of these patterns there was one that dominates: the pattern known as the 'global signal.' It's easy to see when viewing an fMRI scan: suddenly the brain's fMRI signal 'lights up' with strong activity that seems to cover the entire brain—thus, the reason it's called the 'global signal.'"

The primary objective of this recent study by Bolt and his colleagues was to pin-point the underlying physiological and neural sources of the dominant pattern in fMRI signals observed in their earlier work.

To do this, they analyzed human fMRI data collected in previous studies and compiled them into readily available datasets, which are widely used to conduct neuroscience research.

"Most existing datasets are limited—pulse oximeter (PPG) on the finger and respiration belts—while others may collect more comprehensive recordings," explained Bolt.

"Catie Chang had gathered a comprehensive fMRI dataset with a wealth of physiological recordings that allowed us to track a range of bodily states and tie these back to what's going on in the brain, particularly the brain's 'global signal.' We also supplemented these analyses with several other fMRI datasets (with associated physiological recordings) to ensure the robustness of our findings."

The methods employed by the researchers were carefully designed to determine the extent to which the human body's physiological systems (e.g. heart, lungs, exocrine, etc.) track fluctuations in global fMRI signals. Moreover, if these systems are tightly connected, Bolt and his colleagues wished to determine which of them is responsible for the global fMRI fluctuations they observed.

"We found a robust association between the global fMRI signal and a host of autonomic-driven changes in the body that spanned cardiovascular, pulmonary, exocrine and smooth muscle systems under resting conditions," said Bolt.

"We also found that these co-fluctuations of brain and body observed at rest are induced by experimental manipulation of arousal, including a cued deep breath and intermittent auditory stimulation. Further, the same brain and body co-fluctuations were observed with spontaneous arousals during sleep (as measured by brief, aperiodic EEG activation)."

Overall, the findings gathered by Bolt and his colleagues suggest that the autonomic nervous system, which plays a central role in the regulation of arousal and wakefulness, is an important source of the global fMRI signal. Similarly, they also indicate that the global signal in the brain is a key component of the autonomic nervous system's arousal response.

"We would now like to dive into the functional significance of the global fMRI signal in the arousal response—what is it 'doing' for us, and what downstream mechanisms (or behaviors) are affected by this phenomena," added Bolt.

More information: Taylor Bolt et al, Autonomic physiological coupling of the global fMRI signal, *Nature Neuroscience* (2025). DOI: 10.1038/s41593-025-01945-y.
Journal information: Nature Neuroscience

JUNE 16, 2025

Neuroscience drives new well-being app

by University of New South Wales edited by Sadie Harley, reviewed by Andrew Zinin

Researchers from NeuRA and UNSW Sydney have launched a new app aimed at boosting the well-being and resilience of adults. This innovative mobile application, called ReNeuWell, shifts the focus from managing distress to actively promoting mental flourishing, offering a neuroscience-backed, personalized approach to mental health.

Designed by Associate Professor Justine Gatt, director of the Center for Well-being, Resilience and Recovery at NeuRA and UNSW's School of Psychology, ReNeuWell is underpinned by the COMPAS-W Well-being Scale. This validated tool assesses both subjective (hedonic–composure, positivity, life satisfaction) and psychological (eudaimonic—self-worth, mastery, achievements) well-being, providing users with a comprehensive profile.

"The app is designed for anyone looking for ways to understand and boost their own level of mental well-being," states Associate Professor Gatt, emphasizing its role in guiding individuals towards optimal mental health.

ReNeuWell offers a unique personalized program of activities over four-week periods, drawing on psychological concepts such as mindfulness, meditation, self-compassion, and goal-setting.

These activities are tailored to improve specific aspects of a user's well-being, grounded in the COMPAS-W scale's proven link to brain function, genetics, cognitive performance, and even physical health indicators.

A 12-week clinical trial is currently underway, with NeuRA actively recruiting at least 500 adult participants from the general public. Eligible individuals will receive free access to the

app, committing to just 10 minutes of daily use and three short surveys. This trial aims to further validate the app's effectiveness and gather user feedback for refinement.

Developed by Miroma Project Factory, ReNeuWell exemplifies a successful collaboration between research and industry to address real-world mental health needs.

The ReNeuWell app is now available for download on the Apple App Store in Australia for a one-time fee of AUD$24.99 for those who do not wish to participate in the trial.Provided by University of New South Wales

Artificial neural networks reveal how peripersonal neurons represent the space around the body

by Ingrid Fadelli, Phys.org edited by Lisa Lock, reviewed by Robert Egan

Artificial action values create body-part centered fields, which resemble biological peripersonal neurons. a, When objects offer rewards upon contact, agents maximize value by moving toward positive-reward objects (apple) and away from negative-reward objects (wasp). b, Motor repertoire shapes body-part-centered fields. c, An artificial neural network trained on simultaneous interception and avoidance tasks naturally adopts a modular structure, beneficial for use in an egocentric map (left, network graph). d, More subnetwork structure results in better task performance. Credit: Bufacchi et al

The brains of humans and other primates are known to execute various sophisticated functions, one of which is the representation of the space immediately surrounding the body. This area, also sometimes referred to as "peripersonal space," is where most interactions between people and their surrounding environment typically take place.

Researchers at Chinese Academy of Sciences, Italian Institute of Technology (IIT) and other institutes recently investigated the neural processes through which the brain represents the area around the body, using brain-inspired computational models. Their findings, published in *Nature Neuroscience*, suggest that receptive fields surrounding different parts of the body contribute to building a modular model of the space immediately surrounding a person or artificial intelligence (AI) agent.

"Our journey into this field began truly serendipitously, during unfunded experiments done purely out of curiosity," Giandomenico Iannetti, senior author of the paper, told Medical Xpress. "We discovered that the hand-blink reflex, which is evoked by electrically shocking the hand, was strongly modulated by the position of the hand with respect to the eye.

"We soon realized that this blink reflex behaved much like so-called peripersonal neurons, which are neurons that respond to objects near the body. As we got more familiar with the

literature on this type of neuron, however, we noticed that the existing theoretical explanations of their activity fail to explain quite a lot of their properties, such as their modulation by stimulus valence, speed, and motor repertoire."

Rather than collecting new data, which could then be added to the extensive and disjointed data collected during previous studies, Iannetti and his colleagues set out to develop a new quantitative framework that clarifies why the peripersonal neurons observed in earlier experiments exist and how they work. This framework could then be integrated with existing neuroscience theories.

To develop their framework, they employed artificial neural networks (ANNs) trained via reinforcement learning. These are brain-inspired computational models that can learn to complete various tasks with good accuracy, emulating the connections between neurons.

"In simple terms, we built computer simulations of simplified 'animals,' which learned through trial and error to choose actions based on how much reward or punishment those actions would bring over time," explained Rory John Bufacchi, first author of the paper.

"Our approach involved three main steps. First, our key insight was that peripersonal responses might simply reflect the value of potential actions: whether reaching out to or dodging environmental objects would lead to rewards or punishments."

Iannetti, Bufacchi and their colleagues hypothesized that the responses of peripersonal neurons could be associated with assessments of one's immediate surroundings, specifically in terms of the extent to which different actions would lead to rewards or punishments. To test this hypothesis, they trained ANNs to intercept or avoid objects, then tried to determine whether this resulted in similar body-part-centered responses as those previously observed in the human brain.

A large portion of artificial neurons displayed body-part centric responses that shift with the location of the limb. Receptive fields of each artificial neuron are shown as color maps. Units with receptive fields classified as bodypart-centered are highlighted by a black box. Note how the number of bodypart-centered units increases moving from input to output layers. Credit: *Nature Neuroscience* (2025). DOI: 10.1038/s41593-025-01958-7
"We then proposed a theoretical construct, an 'egocentric value map,' which is constructed from groups of peripersonal neurons, forming a more abstract, predictive model of the world near the body that allows rapid adaptation to novel situations," said Bufacchi. "This idea helped us unify our findings with broader theories in computational neuroscience by framing body-centered responses as part of a flexible, predictive model of the nearby environment."

After they had created their "egocentric value map," the researchers compared it to the observations gathered during neuroscience studies performed by multiple labs. The data they compared it to included recordings of the activity of neurons in the brains of macaques, as well as human functional magnetic resonance imaging (fMRI) scans, electroencephalography (EEG) scans and behavioral patterns observed during experiments.

"In brief, we found that the neurons in our artificial agents naturally developed body-part-centered receptive fields that matched empirical findings from biological peripersonal neurons, supporting our theoretical assumptions," explained Iannetti.

"Specifically, these neurons' receptive fields expanded with faster-moving stimuli, tool use, and higher-value objects. The networks of artificial neurons also separated into sub-networks specialized for avoidance and interception, mirroring the modularity of both the macaque brain and the egocentric value map that we propose."

The researchers were ultimately able to demonstrate that a set of peripersonal neurons can in fact create an egocentric map of a primate's surroundings. They then compared the theoretical framework they had developed to previous interpretations of peripersonal neurons and their function.

"Our theory was the only one to successfully fit extensive experimental data, outperforming alternative explanations and providing a generalizable framework for understanding peripersonal responses," said Iannetti.

The recent work by Iannetti, Bufacchi and their colleagues contributes to the understanding of peripersonal neurons in the primate brain and how they map out the environment immediately surrounding the body of primates or humans. Yet the insight gathered by the team could soon also help to advance embodied AI agents, robotic systems and prosthetics,

"These findings have potential applications in fields such as neuroprosthetics and human–robot interactions," explained Iannetti. "For example, robots could simulate egocentric value maps to develop adaptive, context-specific representations of appropriate human interaction distances, making human–robot collaboration more natural and effective."

The researchers are now planning to build on their findings and continue testing the validity of the framework they introduced. In their next studies, they will test the predictions generated by their computational model and try to address some of its shortcomings.

"For example, the model is currently framed in a reinforcement learning perspective, which lacks explicit parameters for sensory uncertainty," added Bufacchi. "We will solve this by using different mathematical framings such as active inference, which explicitly incorporates sensory uncertainty and cognitive modeling of the environment. We also plan to collaborate across labs to model richer, more fine-grained and contemporary neuronal data."

More information: Rory John Bufacchi et al, Egocentric value maps of the near-body environment, *Nature Neuroscience* (2025). DOI: 10.1038/s41593-025-01958-7
Journal information: Nature Neuroscience

JUNE 20, 2025

Brain organizes visuomotor associations into structured graph-like mental schemes, study finds

by Ingrid Fadelli, Phys.org edited by Gaby Clark, reviewed by Robert Egan

Task design and baseline correction. a, Example musical notation and the associated action/key. b, Example visuomotor mapping with the correct key press for each of the eight stimuli and illustration of one specific feature-to-level assignment. Visuomotor mappings were counterbalanced across participants. c, Task schematic for the learning task. d, Task schematic for the RT baseline task. e, Visualization of RT baseline correction, with average RTs for each pairwise transition between fingers for the learning and RT baseline tasks (Experiment 1) depicted as heat maps. Baseline RTs are subtracted from learning task RTs to yield corrected RTs. Credit: Juliana E. Trach & Samuel D. McDougle. (*Nature Human Behaviour*, 2025).

Graphs, visual representations outlining the relationships between different entities, concepts or variables, can be very effective in summarizing complex patterns and information. Past psychology studies suggest that the human brain stores memories and experiences following graph-like and structured patterns, specifically as a network of associations, also referred to as cognitive graphs.

These cognitive graphs are hypothesized to represent different concepts as "nodes" and the relationships between these concepts as edges connecting these nodes. By organizing information in a structured way, they can allow people to apply knowledge they have acquired in the past to new situations and draw conclusions about what is happening based on previous experiences.

The role of cognitive graphs has been widely investigated in the past, with most studies focusing on their contribution to the storage and retrieval of facts and knowledge (i.e., declarative memories). In contrast, the extent to which they influence the planning and control of movements remains poorly understood.

Researchers at Yale University recently set out to investigate the possibility that the human brain also stores memories related to movement as mental graph-like structures, which are then used to plan motor actions in response to visual stimuli. Their paper, published in *Nature Human Behavior*, presents new evidence suggesting that the brain stores visuomotor associations in structured ways and can then retrieve these associations to plan movements in specific situations.

"Much of human memory takes the form of cognitive graphs that allow us to relate and generalize knowledge," wrote Juliana E. Trach and Samuel D. McDougle in their paper. "The influence of structured memory in the motor system is less clear. We examine how structured memory representations influence action selection when responses are retrieved from newly learned, hierarchical visuomotor maps."

As part of their study, the researchers carried out a series of experiments involving 182 participants. These participants were asked to complete a task that required them to press specific buttons in response to different visual cues (e.g., geometrical objects with different shapes or colors) that appeared on a screen.

Theoretical models. Credit: *Nature Human Behaviour* (2025). DOI: 10.1038/s41562-025-02217-2

Notably, they were asked to quickly press a different combination of keys in response to what they saw. For some participants, the associations between what they saw and the keys they were asked to press followed a structured pattern, while for others they were random.

The researchers recorded the time it took for participants to press the correct key combinations. These response times were then analyzed to try to determine whether people were in fact using a mental graph to guide their actions during their experiment.

"Human participants learned visuomotor mappings with (or without) an imposed latent structure that linked visual stimulus features (for example, color or shape) to intuitive motor distinctions, such as hands and pairs of fingers," explained Trach and McDougle.

"In participants who learned structured visuomotor mappings, transitional response times indicated that retrieving the correct response from memory invoked the 'traversal' of a structured mental graph."

In some trials of the experiment, the researchers also asked participants to press the key combinations as fast as possible or at specific times to determine whether their performance changed when under pressure. Overall, the data they collected suggests that associations between visual stimuli and motor actions are represented as mental graphs, which can be retrieved to guide future actions, even under pressure.

"Forced-response experiments revealed similar computations within individual trials," wrote Trach and McDougle. "Moreover, graph-like representations persisted even after multiple days of practice with the visuomotor mappings. Our results point to direct links between

internal computations over structured memory representations and the preparation of movements."

This recent study offers new interesting insights into the contribution of mental graphs to the planning and execution of movements. Future research could help to validate the team's findings, while also potentially examining the role of these structured cognitive representations in a wider range of real-world scenarios.

Written for you by our author Ingrid Fadelli, edited by Gaby Clark , and fact-checked and reviewed by Robert Egan —this article is the result of careful human work. We rely on readers like you to keep independent science journalism alive. If this reporting matters to you, please consider a donation (especially monthly). You'll get an **ad-free** account as a thank-you.

More information: Juliana E. Trach et al, Mental graphs structure the storage and retrieval of visuomotor associations, *Nature Human Behaviour* (2025). DOI: 10.1038/s41562-025-02217-2.
Journal information: Nature Human Behaviour

JUNE 20, 2025

Human–AI collectives make the most accurate medical diagnoses, according to new study

by Nicole Siller, Max Planck Society edited by Lisa Lock, reviewed by Robert Egan

Collective Intelligence in medicine. Credit: MPI for Human Development
Artificial intelligence (AI) can effectively support doctors in making diagnoses. It makes different mistakes than humans—and this complementarity represents a previously untapped strength. An international team has now systematically demonstrated for the first time that combining human expertise with AI models leads to the most accurate open-ended diagnoses. Their paper is published in the *Proceedings of the National Academy of Sciences*.

Diagnostic errors are among the most serious problems in everyday medical practice. AI systems—especially large language models (LLMs) like ChatGPT-4, Gemini, or Claude 3—offer new ways to efficiently support medical diagnoses. Yet these systems also entail

considerable risks—for example, they can "hallucinate" and generate false information. In addition, they reproduce existing social or medical biases and make mistakes that are often perplexing to humans.

The international research team, led by the Max Planck Institute for Human Development and in collaboration with partners from the Human Diagnosis Project (San Francisco) and the Institute of Cognitive Sciences and Technologies of the Italian National Research Council (CNR-ISTC Rome), investigated how humans and AI can best collaborate.

The result: hybrid diagnostic collectives—groups consisting of human experts and AI systems—are significantly more accurate than collectives consisting solely of humans or AI. This holds particularly for complex, open-ended diagnostic questions with numerous possible solutions, rather than simple yes/no decisions.

"Our results show that cooperation between humans and AI models has great potential to improve patient safety," says lead author Nikolas Zöller, postdoctoral researcher at the Center for Adaptive Rationality of the Max Planck Institute for Human Development.

The researchers used data from the Human Diagnosis Project, which provides clinical vignettes—short descriptions of medical case studies—along with the correct diagnoses. Using more than 2,100 of these vignettes, the study compared the diagnoses made by medical professionals with those of five leading AI models.

In the central experiment, various diagnostic collectives were simulated: individuals, human collectives, AI models, and mixed human–AI collectives. In total, the researchers analyzed more than 40,000 diagnoses. Each was classified and evaluated according to international medical standards (SNOMED CT).

Humans and machines complement each other—even in their errors

The study shows that combining multiple AI models improved diagnostic quality. On average, the AI collectives outperformed 85% of human diagnosticians. However, there were numerous cases in which humans performed better. Interestingly, when AI failed, humans often knew the correct diagnosis.

The biggest surprise was that combining both worlds led to a significant increase in accuracy. Even adding a single AI model to a group of human diagnosticians—or vice versa—substantially improved the result. The most reliable outcomes came from collective decisions involving multiple humans and multiple AIs.

The explanation is that humans and AI make systematically different errors. When AI failed, a human professional could compensate for the mistake—and vice versa. This so-called error complementarity makes hybrid collectives so powerful. "It's not about replacing humans with machines. Rather, we should view artificial intelligence as a complementary

tool that unfolds its full potential in collective decision-making," says co-author Stefan Herzog, Senior Research Scientist at the Max Planck Institute for Human Development.

However, the researchers also emphasize the limitations of their work. The study only considered text-based case vignettes—not actual patients in real clinical settings. Whether the results can be transferred directly to practice remains a question for future studies to address. Likewise, the study focused solely on diagnosis, not treatment, and a correct diagnosis does not necessarily guarantee an optimal treatment.

It also remains uncertain how AI-based support systems will be accepted in practice by medical staff and patients. The potential risks of bias and discrimination by both AI and humans, particularly in relation to ethnic, social, or gender differences, likewise require further research.

Wide range of applications for hybrid human–AI collectives

The study is part of the Hybrid Human Artificial Collective Intelligence in Open-Ended Decision Making (HACID) project, which aims to promote the development of future clinical decision-support systems through the smart integration of human and machine intelligence. The researchers see particular potential in regions where access to medical care is limited. Hybrid human–AI collectives could make a crucial contribution to greater health care equity in such areas.

"The approach can also be transferred to other critical areas—such as the legal system, disaster response, or climate policy—anywhere that complex, high-risk decisions are needed. For example, the HACID project is also developing tools to enhance decision-making in climate adaptation," says Vito Trianni, co-author and coordinator of the HACID project.

More information: Nikolas Zöller et al, Human–AI collectives most accurately diagnose clinical vignettes, *Proceedings of the National Academy of Sciences* (2025). DOI: 10.1073/pnas.2426153122
Journal information: Proceedings of the National Academy of Sciences
Provided by Max Planck Society
JUNE 17, 2025

Two brain cell types that determine whether smells are pleasant or unpleasant identified

by University of Florida edited by Gaby Clark, reviewed by Robert Egan

Ventral striatum projecting BLA neurons arise from the BA and are comprised of Drd1+ and Drd2+ neurons. Credit: *Molecular Psychiatry* (2025). DOI: 10.1038/s41380-025-03075-0
You wouldn't microwave fish around your worst enemy—the smell lingers both in kitchen and memory. It is one few of us like, let alone have positive associations with. But what makes our brains decide a smell is stinky?

A new study from UF Health researchers reveals the mechanisms behind how your brain decides you dislike—even loathe—a smell. The findings are published in the journal *Molecular Psychiatry*.

Or as first author and graduate research fellow Sarah Sniffen puts it: How do odors come to acquire some sort of emotional charge?

In many ways, our world capitalizes upon the importance of smells to influence emotions, running the gamut from perfumes to cooking and even grocery store design.

"Odors are powerful at driving emotions, and it's long been thought that the sense of smell is just as powerful, if not more powerful, at driving an emotional response as a picture, a song or any other sensory stimulus," said senior author Dan Wesson, Ph.D., a professor of pharmacology and therapeutics in the UF College of Medicine and interim director of the Florida Chemical Senses Institute.

But until now, researchers have puzzled over what circuitry connects the parts of the brain vital to generating an emotional response with those responsible for smell perception.

The team started off with the amygdala, a brain region that curates your emotional responses to sensory stimuli. Although all our senses (sound, sight, taste, touch and smell) interact with this small part of your brain, the olfactory system takes a more direct route to it.

"This is, in part, what we mean when we say your sense of smell is your most emotional sense," Sniffen said. "Yes, smells evoke strong, emotional memories, but the brain's smell centers are more closely connected with emotional centers like the amygdala."

In the study, researchers looked at mice, who share neurochemical similarities with people. They can learn about odors and categorize them as good or bad.

After observing their behavior and analyzing brain activity, the team found two genetically unique brain cell types that allow odors to be assigned into a bucket of good feelings or bad feelings.

Initially, the team expected that one cell type would generate a positive emotion to an odor, and another would generate a negative emotion. Instead, the brain's cellular organization gives the cells the capability of doing either.

"It can make an odor positive or negative to you," Wesson said. "And it all depends upon where that cell type projects in your brain and how it engages with structures in your brain."

But why is knowing more about how we categorize smells important? Well, for starters, smells—and our reactions to them—are a part of life. Sometimes, however, our reactions to them can be outsized, or take on a negative association so strong it disrupts how we live.

"We're constantly breathing in and out and that means that we're constantly receiving olfactory input," Sniffen said. "For some people that's fine, and it doesn't impact their day-to-day life. They might even think, 'Oh, odors don't matter that much.' But for people who have a heightened response to sensory stimuli, like those with PTSD or anxiety or autism, it's a really important factor for their day-to-day life."

In the future, the research could help clinicians adjust for heightened sensory responses that some people struggle with in their everyday lives, Wesson added. One example? A patient associating a clinic's smell with transfusions that made them queasy.

Based upon the receptor systems in these specific brain pathways, the team members believe they might be able to change those associations.

Potentially, medications could suppress some of these pathways' activity to allow you to overcome stressful and aversive emotional responses.

Conversely, these pathways could be activated to restore enjoyment to things that people might have grown indifferent to—like those who lose their appetite from illness.

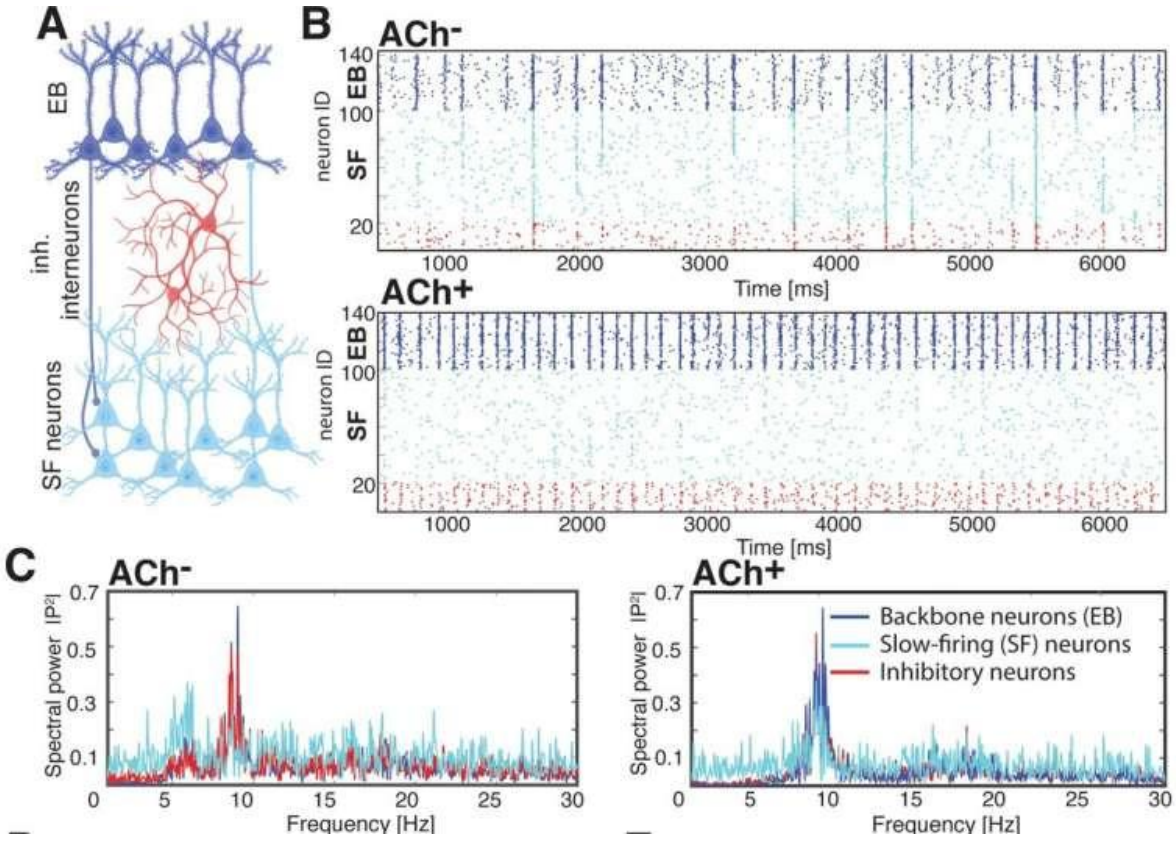
"Emotions in part dictate our quality of life, and we're learning more about how they arise in our brain," Wesson said. "Understanding more about how our surroundings can impact our feelings can help us become happier, healthier humans."

More information: Sarah E. Sniffen et al, Directing negative emotional states through parallel genetically-distinct basolateral amygdala pathways to ventral striatum subregions, *Molecular Psychiatry* (2025). DOI: 10.1038/s41380-025-03075-0
Journal information: Molecular Psychiatry
Provided by University of Florida

JUNE 23, 2025

A universal sleep pattern could help strengthen and separate memories

by Matt Davenport, University of Michigan edited by Stephanie Baum, reviewed by Robert Egan



ACh-regulated current modulates activation of neuron populations during ACh⁻ and ACh⁺ network states. Credit: *PLOS Computational Biology* (2025). DOI: 10.1371/journal.pcbi.1013097

Although we know sleep is essential to our physical and mental well-being, it remains an incredibly enigmatic behavior, scientifically speaking. Researchers at the University of Michigan, however, may have developed a new hypothesis to account for one of sleep's looming mysteries.

Every living thing that sleeps appears to follow the same basic pattern. From wakefulness, organisms transition to a repeating cycle of sleep with low brain activity followed by a stage

where our brains are harder at work, among other things, generating vivid dreams. Humans' eyes also dance around behind our eyelids during that high-activity stage, which is why it's referred to as rapid eye movement (REM) sleep.

Although there are a few notable exceptions—including people with narcolepsy and people who haven't slept in days—this repeating non-REM to REM sleep cycle is remarkably prevalent across the animal kingdom.

"Evolutionarily, it's so preserved and so ubiquitous across species," said Sara Aton, U-M professor of molecular, cellular and developmental biology. "That means there's probably something really important about that particular order of sleep. And it never goes in reverse, unless something has really screwed up the system."

Yet, scientists have lacked a satisfying explanation for the biological function of this virtually universal phenomenon. Now, U-M researchers led by Aton and Michal Zochowski have put together a hypothesis built on experimental observations in mice and computer modeling of the brain's neural circuitry.

That hypothesis posits that if memories were shrubs, the non-REM phase of sleep helps them grow taller and stronger. The REM stage then prunes, keeping them shapely and distinct, and preventing them from overlapping and growing into each other.

"It only works if you have this sequence. If you go in reverse and have REM first, it prunes everything away. Then no memory is left," Aton said. "In the proper sequence, you reinforce things that need to be reinforced. Then REM comes in to prune back the overlapping portions of unrelated memories."

The work is published in the journal *PLOS Computational Biology*.

In mice, the researchers could observe the effect of sleep on remembering simple conditioning experiments. In humans, Zochowski said, this could have familiar implications in our everyday business.

"Let's say you have three meetings in a day. We know that you'll remember these meetings better after a good night's sleep," Zochowski said. "Now, it appears that during non-REM sleep, you're strengthening your memory of each meeting. But you also need to remember who said what and during which meeting. What REM does is keep that separate."

Cycles and circuits

Led by Aton's team, the researchers' latest experiments monitored mice brains to see which parts of the hippocampus were active during different phases of sleep following a simple conditioning scenario.

Mice were moved from their home enclosures to a new environment, and after exploring for a couple minutes, would receive a small shock to their feet. There was also a control group

of mice who experienced no such unpleasantries. This enabled the researchers to compare brain activity of sleeping mice during REM and non-REM cycles that had and hadn't forged an association between the new space and a shock.

But researchers can't yet zero in on all the individual neurons encoding specific memories with available techniques, so this is where the team's modeling stepped in to help complete the picture. The model was developed by Zochowski's group and treats newly encoded memories as changes in the activity of neurons in circuits subject to the brain's environment, where a biochemical called acetylcholine modulates their activity.

"We can actually simulate and pinpoint which neurons are being activated by a learning event," Aton said. "We can model that and we can model changes that happen with respect to acetylcholine as an animal goes through the different stages of sleep."

There are also two types of neurons: excitatory ones that tend to stimulate their neighbors and inhibitory ones that tamp down the activity of others. By combining these dynamics with real world data on brain activity and acetylcholine levels during different phases of sleep, the model helped reveal conclusions that were previously inaccessible.

Although the researchers are excited by the result, they stressed that this is not the final word on the matter. Their circuit model is a simplified representation of the brain and the team's experiments tested relatively straightforward memory scenarios. Thus, the hypothesis could change or evolve as researchers subject it to more complex test cases and provide it with new and different types of data.

"What we have now is a study that says, 'Look, this is what could be happening,'" Zochowski said. "Now we have to prove that the model is associated with reality."

More information: Michael Satchell et al, Cholinergic modulation of neural networks supports sequential and complementary roles for NREM and REM states in memory consolidation, *PLOS Computational Biology* (2025). DOI: 10.1371/journal.pcbi.1013097
Journal information: PLoS Computational Biology
Provided by University of Michigan

JUNE 23, 2025

What is an 'alpha' male?

by Jwana Aziz, Anna Lavis, The Conversation edited by Lisa Lock, reviewed by Andrew Zinin

Credit: Pixabay/CC0 Public Domain

The recent success of the Netflix show Adolescence has drawn attention to misogynistic rhetoric and how it spreads online. Safeline, an organization supporting survivors of sexual abuse, has warned that terms like "high-value" and "low-value men" (also described as "alpha" and "beta" men) are being used to radicalize boys, drawing them into embracing such rhetoric.

Last year, Elon Musk shared a post that argued only "high T alpha males"—men with high testosterone levels—can think freely and are most qualified to lead and govern. Relevant here is the reach of influencers like Andrew Tate, a self-described misogynist who, with his brother, is now facing 21 charges in the UK including rape and human trafficking, all of which they deny.

What do these terms mean, and how harmful are they?

The terms alpha and beta male are pseudoscientific terms used to push a concept of masculinity as necessarily hierarchical and aggressive. The theory frames the ideal of a man as someone who is financially successful, assertive, strong, logical and a "natural" leader.

Acquiring high-value status is not viewed merely as key to success in life, but also for attracting what are seen as high-value—namely virtuous and physically attractive—women, as well.

Common and serious use of terms like alpha or high-value male were once largely confined to niche internet subcultures like the manosphere and incel (involuntary celibate) forums. But they have broken into the mainstream through influencers like Tate, whose followers describe him as "Top G."

Changing norms?

There are also signs that the ideas around what it means to be "high value" are changing from the traditional, hegemonic view of masculinity. An interesting case study is Ashton Hall, whose morning routine video recently garnered millions of views on TikTok, and was widely discussed online.

The male self-improvement influencer's meticulously structured day comprises a series of self-optimization tasks, starting with push-ups at 4am, journaling by 4.40am, and dunking his face in ice water before hitting the gym at 6.20am. After another ice-water face plunge and some hours of work, the video ends with a woman presenting him with his evening meal.

It is interesting to see Hall take practices traditionally seen as feminine, like journaling and skincare, and embrace them as part of an otherwise very traditionally masculine morning routine.

Another hypermasculine influencer, Hamza, also blends his tough man demeanor with practices like meditation, nutrition and wellness. He frames these habits as "warrior training." Such practices, then, are not viewed as feminine or emasculating.

Masculinity today is influenced by neoliberal ideals, where a man's value is measured by his productivity and success. Practices like self-care are branded as discipline and performance-enhancing tools, used to construct the most optimized, competitive version of the male self.

Ashton Hall may not describe himself as an "alpha male," but in many respects he embodies the idealized neoliberal archetype of masculinity: physical strength, wealth and material possessions.

While Tate's displays of wealth and women are clear performances of masculine dominance, Hall's more restrained approach fits within the same hierarchy. In both, "value" is defined by discipline, social ascendancy and power, especially over women. In Hall's video, it is a woman's hands that can be seen preparing and serving his food, reinforcing traditional gender roles.

Why is it harmful?

It's important to note that not all hypermasculine influencers are necessarily bad role models for young men and boys.

But, as we have explored in a recent report, self-improvement content can be a key gateway into the misogynistic digital space of the manosphere.

In our analysis of online discussions, we found that many of those drawn to hypermasculine influencers reported struggling with various offline vulnerabilities. These included experiencing big life changes, anxiety, depression, bullying and social isolation, and also being neurodiverse. Young followers described motivational content as having "saved" them. Others came across this content through otherwise innocuous searches about getting better abs or finding a girlfriend.

One 15-year-old in our research, for example, recalled being severely bullied at school. He said that after adopting a strict routine inspired by Tate (waking at 6 am, pursuing fitness, cutting out social media), "Now people respect me."

Initially, what young men find may boost their confidence. But in encountering the promotion of unrealistic standards for self-improvement and a "hustle culture" mentality, they may be indoctrinated into an online world of rigidity and misogyny.

Assigning worth to men based on social and economic status has personal and societal consequences. It presents failure to meet these standards as a path to loneliness and suffering, and frames following self-improvement influencers as the only solution.

The appeal of self-improvement lies in its promise of transformation—from a state of dissatisfaction and unfulfillment to one of abundance, empowerment and power. Even followers of Tate's who say they don't agree with his views of women are drawn to his financial and business success.

While presented as aspirational, being "high-value" is typically reserved to those with privileges of time and wealth, making it inherently exclusive and inaccessible to most. More importantly, it encourages a worldview where people are judged not for who they are, but for rather how much they produce and what they can offer.

Such rhetoric reduces human relationships to metrics-based transactions based on a hierarchical order where only those who have accumulated the most power, wealth, and success rise to the top. Andrew Tate's "Top G" persona rests on this understanding of human relations, resulting in a hyper-competitive transactional model of masculinity.

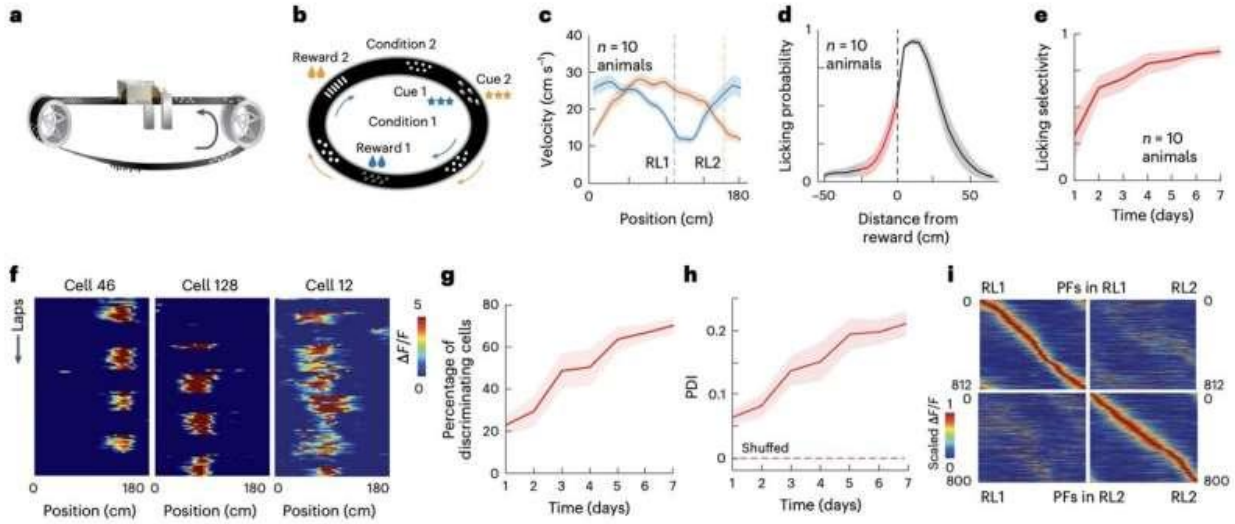
More concerning is the ease through which this discourse lends itself to misogynistic narratives. In one video, Tate describes how a "body count [the number of sexual partners] is the easiest way to judge the value of a woman."

This metric, which men are exempted from, becomes the standard that men can use to assess and demean women. It reveals the true intentions behind concepts such as "high value"—a way to rank men and justify the control and devaluation of women, further reinforcing systems of power and male dominance.

JUNE 25, 2025

How hippocampal place cells and synaptic plasticity contribute to the progressive acquisition of memories

by Ingrid Fadelli, Phys.org edited by Stephanie Baum, reviewed by Robert Egan



Daily evolution of behavior and single-neuron and population activity. a,b, Schematics of the experimental apparatus (a) and two different cue–RL conditions (b). c, Average velocity profiles for mice during condition RL1 (blue; shading indicates s.e.m.) and RL2 (orange) on day 7. Note the selective slowing near RLs. d, Licking probability in reference to RLs with anticipatory licking shown in red for day 7. e, Licking selectivity (Methods) as a function of

behavior day. f, Example PCs with RL2 preference (left), RL1 preference (middle) and no preference (right). g, Percentage of PCs showing increased cell discriminability across experimental days. h, PDI increases with experimental day. The dashed line shows the PDI for shuffled data. i, Heat maps of PCs with PF activity in condition RL1 (top) and during RL1 (top left) and RL2 (top right; both sorted by activity during RL1). Bottom, same as the top but for PCs with PFs active in condition RL2 (sorted by activity during RL2). Data are presented as mean ± s.e.m. in c–e, g and h. Credit: *Nature Neuroscience* (2025). DOI: 10.1038/s41593-025-01986-3

The human brain is known to store various memories for long periods of time, progressively learning from new experiences and forming adaptive representations that ultimately guide decision-making and behavior. When people experience new things, their brain creates new memories and mental representations, without overwriting or deleting old ones.

Many past neuroscience studies have tried to uncover the neural processes underpinning this progressive acquisition of new memories over the course of the human lifespan. While the findings collected so far have improved the overall understanding of memory encoding and consolidation, the mechanisms through which the brain stores new memories without overwriting older ones have not yet been fully elucidated.

Researchers at Baylor College of Medicine recently carried out a study aimed at further exploring these neural mechanisms, specifically looking at the activity of place cells in the CA1 region of the hippocampus, neurons that become active when an animal or human is in a specific location.

Their findings, published in *Nature Neuroscience*, suggest that to retain old memories while also enabling the formation of new ones, the brain progressively modifies connections between neurons via a process known as synaptic plasticity.

"How brain networks connected by labile synapses store new information without catastrophically overwriting previous memories remains poorly understood," wrote Sachin P. Vaidya, Guanchun Li and their colleagues in their paper. "To examine this, we tracked the same population of hippocampal CA1 place cells (PCs) as mice learned a task for 7 days."

The researchers carried out an experiment involving adult mice that were trained to complete a behavioral task. This task required them to run on a treadmill to receive water rewards, while learning to interpret light cues and behave accordingly to receive greater rewards.

As the mice learned to complete the task, Vaidya, Li and their colleagues tracked the activity of place cells in the CA1 region of the animals' hippocampi, using a technique known as calcium imaging. This is a widely used method that allows neuroscientists to detect when neurons are active, using genetic tools that cause cells to light up when calcium enters them, and a tiny microscope implanted in the mouse brain, which can be used to observe neurons and when they light up.

"We found evidence of memory formation as both the number of PCs maintaining a stable place field and the stability of individual PCs progressively increased across the week until most of the representation was composed of long-term stable PCs," wrote the researchers.

"The stable PCs disproportionately represented task-related learned information, were retrieved earlier within a behavioral session and showed a strong correlation with behavioral performance. Both the initial formation of PCs and their retrieval on subsequent days were accompanied by prominent signs of behavioral timescale synaptic plasticity (BTSP), suggesting that even stable PCs were re-formed by synaptic plasticity each session."

Essentially, the researchers found that some place cells became more stable and remained active at the same sites while the mice were learning the behavioral task. These "stable" cells appeared to encode information that was important for the completion of the experimental task, as they were activated early each time the mice started a new learning session.

The team's results suggest that while the activity of some place cells was more stable, the connections between them were not. Instead, they adapted over time as the mice engaged in different behaviors, via a fast process known as BTSP.

"Further experimental evidence supported by a cascade-type state model indicates that CA1 PCs increase their stability each day they are active, eventually forming a highly stable population," wrote the researchers. "The results suggest that CA1 memory is implemented by an increase in the likelihood of new neuron-specific synaptic plasticity, as opposed to extensive long-term synaptic weight stabilization."

The experiments carried out by this research team shed some new light on the processes that could allow the brain to learn new information without erasing older memories. The findings they gathered could be validated and explored further in additional experiments involving mice or other species.

Eventually, the team's efforts could help scientists and physicians to better understand some memory-related diseases, potentially helping to devise new treatments to prevent memory loss. In addition, they could inform the development of machine learning techniques and other computational models designed to emulate how the brain stores memories and learns new information.

More information: Sachin P. Vaidya et al, Formation of an expanding memory representation in the hippocampus, *Nature Neuroscience* (2025). DOI: 10.1038/s41593-025-01986-3

Journal information: Nature Neuroscience

WHAT THE HUMAN BRAIN SEES THAT AI CAN'T: NEW STUDY REVEALS OUR UNIQUE EDGE IN NAVIGATING THE WORLD

TIM MCMILLAN·JUNE 23, 2025

Most of us have probably never paused to consider the awe-inspiring complexity of our brain's ability to effortlessly decide whether to walk, climb, or swim when encountering a new environment. In an instant, without conscious thought, our brains size up a scene and tell us how we can move through it, a feat that even the most advanced AI systems struggle to replicate.

However, according to new research, this remarkable ability we take for granted daily relies on specialized neural processes that artificial intelligence has yet to replicate despite its rapid advances.

Researchers from the University of Amsterdam have uncovered how the human brain encodes so-called "locomotive action affordances"—the opportunities for movement that our surroundings present.

Published in *PNAS Neuroscience*, their work provides fresh insights into how our brains instantly recognize whether we can walk through a field, climb over rocks, or dive into water, all at a glance.

Perhaps most strikingly, the study highlights how deep neural networks (DNNs)—AI systems inspired by biological brains—fail to replicate this fundamental aspect of human perception.

The team's findings point to a profound difference between natural and artificial intelligence, with implications for everything from robotics to self-driving cars. While AI systems have made enormous

strides in recognizing objects and classifying scenes, they still fail to understand what those scenes afford regarding physical action.

“Even the best AI models don’t give exactly the same answers as humans, even though it’s such a simple task for us,” study co-author and computational neuroscientist Dr. Iris Groen explained in a press release. “This shows that our way of seeing is deeply intertwined with how we interact with the world.”

“We connect our perception to our experience in a physical world. AI models can’t do that because they only exist in a computer.”

The researchers combined brain imaging, behavioral studies, and machine learning analysis to explore this capability. Volunteers in the study were shown images of indoor and outdoor environments, and their brain activity was monitored using functional MRI (fMRI).

Sample of images shown during experiments. (Image Source: University of Amsterdam, Bartnik, et al.)

The goal was to map how the brain represents different locomotive possibilities, such as walking, climbing, swimming, crawling, jumping, or flying.

“We wanted to know: when you look at a scene, do you mainly see what is there – such as objects or colors – or do you also automatically see what you can do with it,” Dr. Groen explained. “Psychologists call the latter ‘affordances’ – opportunities for action; imagine a staircase that you can climb or an open field that you can run through.”

The data revealed that specific regions of the human visual cortex—especially those areas responsible for processing scenes—light up in patterns that directly encode the types of movement possible in a given environment.

Intriguingly, these patterns were distinct from those activated by other properties, such as recognizing objects, surfaces, or general scene categories. This suggests that our brain carves out a separate space to understand how we can act within our surroundings.

In parallel, the researchers tested a variety of deep neural networks trained on everyday visual tasks like object recognition or scene classification. These AIs could identify whether an image depicted a kitchen, a forest, or a city street—but they didn't do well at perceiving what movements those environments allowed.

Results showed that the alignment between AI activations and human brain patterns was weak in locomotive affordances, even though it was strong for object-related tasks.

The team then tried fine-tuning these AI models, training them to classify images by affordance or using language embeddings focused on action possibilities.

While this improved the alignment somewhat, none of the tested systems fully captured the nuanced way human brains represent locomotive possibilities. The gap between human and machine perception remains wide, at least in this domain.

"When trained specifically for action recognition, they could somewhat approximate human judgments, but the human brain patterns didn't match the models' internal calculations," Dr. Groen said.

One of the study's key takeaways is that understanding how we navigate the world requires more than recognizing what's in it—it requires grasping what we can do within it. Our brains manage this automatically, without conscious thought and without needing explicit instructions.

"Our results suggest that locomotive action affordance perception in scenes relies on specialized neural representations different from those used for other visual understanding tasks," the researchers wrote. "Training DNNs directly on affordance labels or using affordance-centered language embeddings increases alignment with human behavior, but none of the tested models fully captures locomotive action affordance perception."

The study opens new and exciting avenues for improving artificial intelligence systems, particularly those designed to operate in

dynamic environments. Better models of affordance perception could revolutionize self-driving vehicles, delivery robots, and even AI assistants in virtual environments, allowing them to interact with the world in more human-like ways. The potential impact of this research on AI's future is hopeful and exciting.

For now, the work underscores how much we still have to learn from our own biology. AI may have surpassed human capabilities in specific tasks like playing chess or analyzing massive data sets.

However, we remain far ahead when it comes to the intuitive understanding of space and movement—something that allows a child to clamber over playground equipment or an adult to navigate a crowded city street. This underscores the need for further research and development in AI to bridge this gap.

The results also remind us that intelligence is more than data processing or pattern matching. The human brain sees possibilities for action, weaving together perception and potential in ways that today's artificial minds are only beginning to grasp.

Studies like this will be essential as AI researchers work to bridge this gap. Scientists hope these new insights will help inspire the next generation of AI systems—ones that can navigate the world with greater efficiency and energy savings, much like the human brain.

"Current AI training methods use a huge amount of energy and are often only accessible to large tech companies," Dr. Groen said. "More knowledge about how our brain works, and how the human brain processes certain information very quickly and efficiently, can help make AI smarter, more economical, and more human-friendly."

JUNE 26, 2025

New instrument for enhanced imaging of nerve fibers in the brain

by Erhard Zeiss, Jülich Research Centre edited by Lisa Lock, reviewed by Andrew Zinin

Nerve fiber pathways Nerve fiber tracts in three brain regions, color-coded. The scattering polarimeter combines the measured fiber directions of ComSLI and 3D-PLI (right), resulting in a better signal than with ComSLI alone (left). The improvement is particularly noticeable in regions with few nerve fibers and leads to fewer erroneous directions (vector maps bottom left). Credit: *Scientific Reports* (2025). DOI: 10.1038/s41598-025-02762-w
In order to understand the structure and functioning of the brain, neuroscientists need to study the complex, three-dimensional pathways and connections of nerve fibers. The intersection of multiple nerve fibers poses a particular challenge for neuroimaging.

Until now, two methods—3D-PLI and ComSLI—have been used separately. Researchers from Jülich and Delft have developed a system that combines both methods to great advantage. They present their "Scattering Polarimeter" in a recent study published in the journal *Scientific Reports*.

Advantages of the combination

3D Polarized Light Imaging (3D-PLI) makes it possible to visualize the course of nerve fibers in entire histological brain sections with a resolution in the micrometer range using visible light. However, the method leaves uncertainties in pixels that contain intersecting nerve fibers. This problem can be solved with the help of Computational Scattered Light Imaging (ComSLI): The same brain slices are illuminated (now automated) from different angles and the transmitted (scattered) light is measured under normal incidence.

This produces light intensity profiles that reveal the underlying brain tissue structure and thus the crossing of nerve fibers. A combination of both methods in a single device would offer decisive advantages: faster measurements, pixel-by-pixel mapping and cross-validation of fiber courses.

The Scattering Polarimeter, potential applications and JUPITER

To this end, the researchers developed the "Scattering Polarimeter" based on the so-called Mueller polarimeter: a microscope that enables simultaneous 3D-PLI and ComSLI measurements during large-scale brain scans.

Initial studies of brain slices from different species using the Scattering Polarimeter have already shown results comparable in quality to the individual measurements of 3D-PLI and ComSLI, and can be used for high-precision multimodal maps of nerve fiber tracts. The scientists now see good opportunities for the micrometer-precise reconstruction of neural networks of the human brain. The capacities of the new Jülich exascale computer JUPITER will also be used for this purpose.

More information: Franca auf der Heiden et al, Scattering polarimetry enables correlative nerve fiber imaging and multimodal analysis, *Scientific Reports* (2025). DOI: 10.1038/s41598-025-02762-w
Journal information: Scientific Reports
Provided by Jülich Research Centre

JUNE 26, 2025

Neurodisability in children linked to increased vulnerability to 'school to prison pipeline'

by Tom Seymour, University of Exeter edited by Sadie Harley, reviewed by Andrew Zinin

Children with special educational needs (SEN) are more likely to be excluded from school, which new studies have found to have a direct link to early criminal convictions.

A research team from the University of Exeter has investigated the "school to prison pipeline," finding SEN may be a pathway to over-representation in youth justice systems. SEN includes neurodisability, which is an umbrella term for conditions affecting the brain and nervous system, including autism, acquired brain injury, attention-deficit hyperactivity disorder (ADHD), dyslexia, and dyspraxia.

The study, "School to prison pipelines: Associations between school exclusion, neurodisability and age of first conviction in male prisoners," published in *Forensic Science International: Mind and Law*, looked at the connection between school exclusions and early involvement with the criminal justice system.

Researchers examined data from 3,000 adults in prison and found prisoners with poorer scores on a neurodisability screener were more likely to have been excluded from school. The more times individuals had been excluded from school, the younger they were when first convicted of an offense.

When children are permanently excluded from school, they are often educated in a Pupil Referral Unit—an alternative education provision for children who can't attend mainstream school. The research also found any prisoners sent to a Pupil Referral Unit were first convicted six years younger than those never excluded from school.

Lead researcher Dr. Hope Kent from the University of Exeter said, "This finding is significant, because six years is the difference between criminal justice contact at age 12 versus 18—which greatly impacts life chances after that conviction and not getting stuck in the 'revolving door' of crime. SEN is also likely under-diagnosed in this group, who may have just been seen as naughty from a young age."

The rate of fixed-term and permanent school exclusions in the UK has been rising since 2012/13. Previous research has shown that school exclusion is associated with negative psychosocial outcomes, including poorer mental health, unemployment, and homelessness. Children with an identified SEN represent 15% of the school population but make up 47% of all permanent exclusions and 45% of fixed-term exclusions.

Researchers noted that while the study provides valuable insights, future research should focus on longitudinal studies to establish causal relationships between school exclusions, neurodisability, and criminal justice involvement.

'Double disadvantage'

A second study, "Neurodevelopmental profile and poverty in primary school confer a 'double disadvantage' in risk of criminal justice system contact by the age of 16: A national prospective cohort study," published in *Longitudinal and Life Course Studies*, has found children with a neurodevelopmental delay and living in poverty (defined as being eligible for free school meals) at age four or five are more vulnerable to criminal justice system contact by age 15.

The research, which analyzed data from 519,920 children born in 2001/02, found these two risk factors independently increase the likelihood of criminalization, and together create a "double disadvantage."

Dr. Kent continued, "To tackle youth crime, we need more SEN support for children to help them succeed in mainstream school, including improved resources to support teachers. We need to think of more ways to keep children engaged and included in education, rather than punishing and excluding them for not fitting into the system we have designed and labeling them as badly behaved from a young age.

"Our findings underscore the need for a dual approach of targeted educational support for children with neurodevelopmental delays, and policy changes to reduce child poverty. Investing in public health and changing welfare policies should go hand-in-hand with providing individual support for children."

Researchers recommend future studies should explore the relationship between poverty and other factors on routes into the criminal justice system for these children.

More information: Hope Kent et al, School to prison pipelines: Associations between school exclusion, neurodisability and age of first conviction in male prisoners, *Forensic Science International: Mind and Law* (2023). DOI: 10.1016/j.fsiml.2023.100123

Hope Kent et al, A 'double disadvantage': neurodevelopmental profile and poverty confer synergistic risk of youth justice involvement, *Longitudinal and Life Course Studies* (2025). DOI: 10.1332/17579597Y2025D000000052
Journal information: Forensic Science International
Provided by University of Exeter

Injury to specific brain connections could explain some people's criminal behavior, study finds

JUNE 27, 2025

by Ingrid Fadelli, Phys.org edited by Sadie Harley, reviewed by Andrew Zinin

Researchers applied multiple techniques to determine the brain connections associated with new onset criminal behavior. Credit: Isaiah Kletenik, MD / Center for Brain Circuit Therapeutics, Brigham and Women's Hospital.

Over the past decades, some lawyers have started using brain imaging scans as evidence during criminal trials, to provide a possible explanation for the criminal behavior of defendants. This was justified by recent neuroscientific studies, which found that some people who commit crimes present differences in specific parts of the brain. Yet a key question remains: are these brain changes causal, compensatory or incidental to the behavior?

To answer this question, researchers at Brigham and Women's Hospital, Harvard Medical School and other institutes in the U.S. analyzed the locations of brain injury temporally associated with a new onset of criminality.

They found evidence suggesting that lesions to a specific white matter tract could be causally implicated in the behavior of individuals who start committing crimes after injury.

Their findings, published in *Molecular Psychiatry*, could help inform future juridical and medical practices, helping lawyers, judges and neurologists to identify individuals who

might have been prompted to commit crimes as a result of injuries, strokes or other diseases.

"During my Behavioral Neurology training I had the unique opportunity to evaluate patients who began committing acts of violence with the onset of brain tumors or degenerative diseases," Isaiah Kletenik, MD and first author of the paper, told Medical Xpress.

"While it is generally accepted that brain injury can lead to problems with memory or motor function, the role of the brain in guiding social behaviors like criminality is more controversial as it touches on the concepts of moral culpability and free will.

"These clinical cases prompted my curiosity into the brain basis of moral decision-making and led me to learn new network-based neuroimaging techniques at the Center for Brain Circuit Therapeutics at Brigham and Women's Hospital and Harvard Medical School."

The primary objective of the recent study by Kletenik and his colleagues was to pin-point specific patterns of brain injury that are associated with newly exhibited violent and criminal behavior, particularly in individuals that were previously unaggressive and law-abiding.

To unveil these patterns, they studied rare clinical cases, specifically those from patients who started committing crimes after a brain injury.

Brain injury to a specific brain connection, the right uncinate, was the most consistent finding among those who developed criminal behavior, particularly violent offenses. Credit: Isaiah Kletenik, MD / Center for Brain Circuit Therapeutics, Brigham and Women’s Hospital.
"We mapped the locations of brain injury from 17 cases of lesion-induced criminality and calculated the structural connections from a large brain atlas derived from 178 healthy controls," explained Kletenik. "We then compared the connections associated with criminality to 706 control lesions from brain injuries associated with other symptoms such as memory loss or depression."

When they analyzed the imaging data of the 17 patients and compared it to that of individuals with no history of criminality, Kletenik and his colleagues uncovered a pattern of brain injury that appeared to be most strongly linked to the emergence of criminal behavior, particularly violent offenses. This pattern was characterized by lesions to a specific white matter tract known as the right uncinate, which connects brain regions responsible for emotion processing with other regions involved in decision-making.

"Structural brain imaging is increasingly being introduced as evidence in criminal trials, yet there is limited scientific research to guide how such data is interpreted," said Kletenik.

"A key question in the courtroom is often whether a specific white matter brain injury identified on a brain scan is incidental, correlated or causal to a behavior. Our results suggest that if an individual has a new brain injury to specific white matter locations, especially to the right uncinate fasciculus, and has new onset criminal behavior, there is an increased likelihood that the injury plays a causal role in the behavior."

The results of this recent study suggest that lesions to the right uncinate fasciculus, whether as a result of physical trauma or a disease, can help to explain why some injured individuals suddenly start committing crimes.

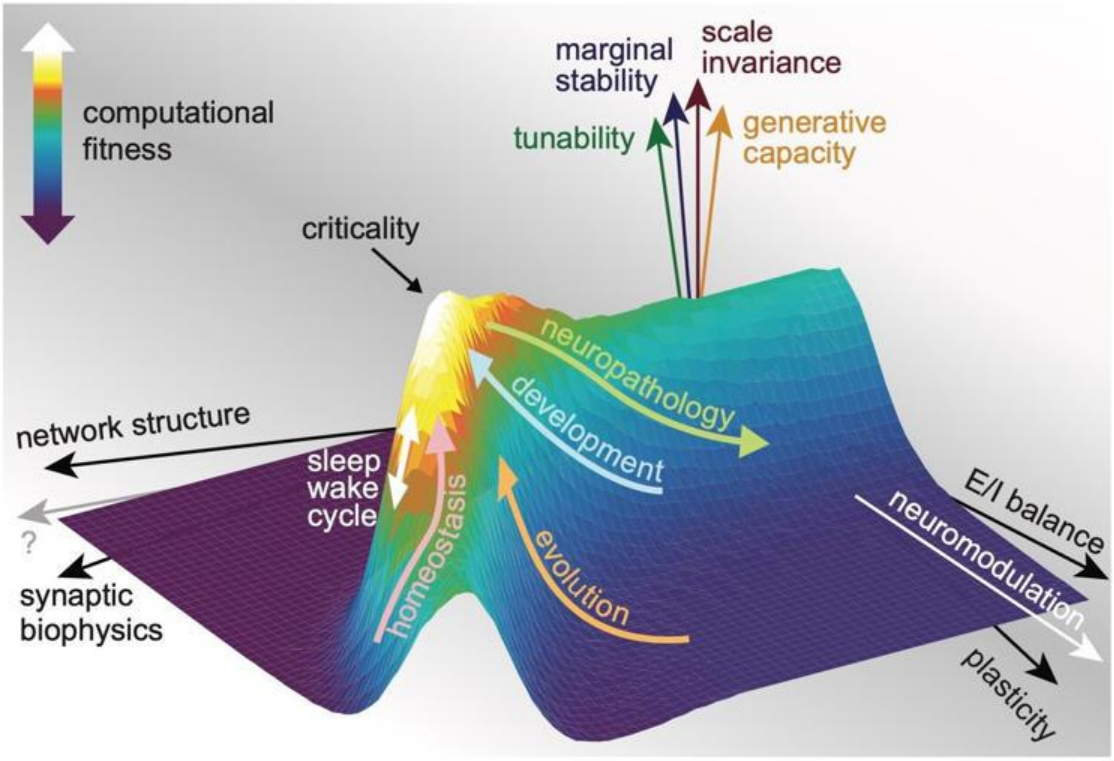
Further research could examine the link between these specific lesions and criminal behavior, potentially examining an even larger pool of clinical cases.

"These findings can help assess whether focal brain injuries may be implicated in new-onset criminality and contribute to our growing knowledge about how social behavior is mediated by the brain," added Kletenik.

Written for you by our author Ingrid Fadelli, edited by Sadie Harley , and fact-checked and reviewed by Andrew Zinin —this article is the result of careful human work. We rely on readers like you to keep independent science journalism alive. If this reporting matters to you, please consider a donation (especially monthly). You'll get an **ad-free** account as a thank-you.

More information: Isaiah Kletenik et al, White matter disconnection in acquired criminality, *Molecular Psychiatry* (2025). DOI: 10.1038/s41380-025-03076-z
Journal information: Molecular Psychiatry

A unified theory of the mind could be key to understanding brain function and neurological disease



According to Keith Hengen and Woodrow Shew, criticality—a state shaped by evolution, growth, and restorative sleep—marks the peak of the brain's computational power. Credit: Neuron (2025). DOI: 10.1016/j.neuron.2025.05.020

In a new paper with implications for preventing Alzheimer's disease and other neurological disorders, Keith Hengen, an associate professor of biology in Arts & Sciences at Washington University in St. Louis, suggests a new comprehensive approach to understanding how the brain works and the rules it must follow to reach optimal performance.

But how is a collection of neurons capable of learning? Hengen suggests that brains become learning machines only when they reach a special state called "criticality." A concept borrowed from physics, criticality describes a complex system that is at the tipping point between order and chaos. At this razor's edge, brains are primed to gain new information, Hengen said. "Brains need to reach criticality to think, remember and learn."

Hengen proposed criticality as a unifying theory of brain function and disease in the journal *Neuron*. Woodrow Shew, a physicist at the University of Arkansas, is the co-author.

A biologist and a physicist may seem like an odd pairing, but the new unifying theory blends both realms of science. Physicists often describe criticality using the classic example of a sand pile: As sand is added, the pile will grow steeper and steeper until it eventually avalanches. Right before that final grain triggered a moment of chaos, the pile was at a critical angle, one step away from instability.

Shew explained that physicists first developed a deep understanding of criticality as a way to describe magnets and other materials. Around the turn of the 21st century, these ideas were expanded to explain a broader range of complex systems, including avalanches, earthquakes and, ultimately, living systems and the brain.

A new understanding of disease

The criticality framework offers a new perspective for understanding neurological disease. Rather than focusing on specific damaged brain regions or accumulated proteins, Hengen argues that diseases such as Alzheimer's destroy something more basic: the brain's ability to maintain criticality.

"Alzheimer's and other neurodegenerative diseases don't just damage neurons, they break the brain's general ability to compute by slowly dissolving criticality," Hengen explained. "As a brain moves further and further from criticality, it loses the ability to adapt and process information effectively."

This framework explains a puzzling feature of brain diseases: Patients often appear completely normal until they've lost many neurons. "The brain has remarkable compensatory abilities that can mask functional problems even as criticality begins to erode," Hengen said. "Traditional assessments miss the early stages because they focus on established endpoints that the brain tries to maintain through workarounds."

As criticality gradually deteriorates, the brain works harder to achieve the same cognitive outcomes, Hengen said. "It's like an engine that still runs but requires more fuel and generates more heat. By the time we notice memory problems or other symptoms, criticality has likely been compromised for years."

Hengen's collaboration with David M. Holtzman, MD, the Barbara Burton and Reuben M. Morriss III Distinguished Professor at WashU Medicine, has revealed that tau protein buildup in Alzheimer's directly disrupts criticality, providing a clear link between the disease's molecular hallmarks and cognitive collapse.

This connection between criticality and Alzheimer's opens exciting diagnostic possibilities. In theory, a simple fMRI could help detect breakdowns in criticality years before symptoms appear. "In combination with cutting-edge blood tests, we could identify people at risk and intervene before irreversible damage occurs," Hengen said.

In another collaboration, Hengen has teamed up with Deanna Barch, the Gregory B. Couch Professor of Psychiatry at WashU Medicine and a professor of psychological and brain sciences in Arts & Sciences, for an observational study to see how criticality at birth determines cognitive development and abilities in childhood.

"From the beginning, some kids are closer to criticality than others, which, based on our theory, suggests they are going to be better learners," Hengen said. "Many outside factors can affect their success in school, but criticality can explain an impressive amount of the variability between children."

The sleep-mind connection

In early 2024, Hengen and co-author Ralf Wessel, a professor of physics in Arts & Sciences at WashU, used the concept of criticality to revisit an age-old question: Why do we need sleep? By tracking brain activity over multiple weeks, they found that sleep restores a state of criticality. "Being awake and active moves us away from criticality, and sleep is like a reset button," Hengen explained.

That insight could help researchers unlock the power of sleep as a therapy for Alzheimer's and other neurological diseases that push the brain away from its optimal state. Previous studies by Holtzman and others have found that people who don't get the sleep they need—perhaps due to shift work or chronic insomnia—are at a much higher risk for Alzheimer's as they age. And there's already some evidence that sleep interventions can help slow the progression of Alzheimer's symptoms.

Hengen believes that targeted, intensive sleep-based therapy could help restore criticality and improve learning and memory in people with brain disease. Studies of mice conducted by Holtzman and James McGregor, a postdoctoral researcher in Hengen's lab, offer a glimpse of the possibilities: Mice specifically bred to have symptoms of Alzheimer's become faster learners after a targeted sleep intervention reinforces criticality.

Critical future

There is much work to be done, but Hengen would eventually like to understand how criticality helps explain complex features of human neurobiology. "We may find that someone who is an amazing artist, for example, might be extremely close to criticality in parts of the brain involved in creative ideation," he said. It's also possible that a close look at criticality could point to undiscovered tendencies or talents that just need an outlet. "Maybe they never tried art, but we can see that the potential is there."

In the meantime, Hengen, Shew, and others are spreading the word about the importance of criticality. Hengen presented a TEDx talk on the subject in 2024 and shared his work at Arts & Sciences' inaugural research pitch competition, where he took second place. He hopes the new *Neuron* paper will inspire conversations among neurologists, doctors, reporters and the general public.

A unified theory of the mind could change the world, but first, it must unify the experts. "Woody (Shew) and I really think we're on to something here," Hengen said. "And, perhaps slowly, others are starting to agree."

WashU was the ideal place for a new concept of the brain to emerge, Hengen said. "We're surrounded by brilliant people in diverse fields, including physics, biology, psychology, mathematics and neuroscience, and the community here is remarkably supportive," he said. "Everyone is ready to help."

More information: Keith B. Hengen et al, Is criticality a unified setpoint of brain function?, *Neuron* (2025). DOI: 10.1016/j.neuron.2025.05.020

Provided by Washington University in St. Louis

This story was originally published on Medical Xpress

Disconnecting helps your brain learn faster

A study reveals that our moments of mental wandering could prepare the brain to learn more effectively. Far from being wasted time, this passive exploration would build internal models of the world.

This discovery, published in Nature, emerges from observing mice navigating virtual environments. Researchers at the Janelia Research Campus recorded the activity of tens of thousands of neurons, revealing a previously unknown mechanism: the visual cortex encodes visual patterns without a specific goal, thereby optimizing future learning.

Exploration, fertile ground for learning

The experiment conducted by the researchers compared two groups of mice moving through a virtual corridor with multiple textures. The first group received rewards (water) by associating certain textures with positive stimuli, while the second explored the same environment without any goal or reward.

Using an advanced imaging technique, the activity of nearly 90,000 neurons was recorded simultaneously. The results show that mice in both groups developed similar neural plasticity in their medial visual cortex, a key region for pattern processing.

The surprise came from the subsequent learning speed: mice that simply explored the environment without rewards learned faster to associate textures with rewards in a follow-up task. This suggests that passive exposure prepares the brain to efficiently encode new information, even without immediate motivation.

Two complementary systems

The study distinguishes two mechanisms: unsupervised learning (automatic, via exposure) and supervised learning (goal-driven). The first creates a neural database, while the second associate’s meanings with it.

Researchers used a two-photon excitation microscope to track neuron activity simultaneously. The data show that medial visual areas activate during passive exposure, while frontal zones only respond to reward-based tasks.

This duality could explain why some learning, such as image recognition or spatial navigation, seems intuitive. The brain would capitalize on pre-established models during exploration, accelerating later training phases.

Article author: Cédric DEPOND

JUNE 29, 2025 FEATURE

Individual neurons in amygdala and hippocampus encode visual features that help recognize faces, study finds

by Ingrid Fadelli, Phys.org edited by Gaby Clark, reviewed by Robert Egan

Feature-based neuronal coding of face identities. Credit: *Nature Human Behaviour* (2025). DOI: 10.1038/s41562-025-02218-1
Humans are innately capable of recognizing other people they have seen before. This capability ultimately allows them to build meaningful social connections, develop their sense of identity, better cooperate with others, and identify individuals who could pose a risk to their safety.

Several past studies rooted in neuroscience, psychology and behavioral science have tried to shed light on the neural processes underlying the ability to encode other people's identities. Most findings collected so far suggest that the identity of others is encoded by neurons in the amygdala and hippocampus, two brain regions known to support the processing of emotions and the encoding of memories, respectively.

Based on evidence collected in the past, researchers have concluded that neurons in these two brain regions respond in specific ways when we meet a person we are acquainted with, irrespective of visual features (i.e., how their face looks). A recent paper published in *Nature Human Behaviour*, however, suggests that this might not be the case, and that individual neurons in the amygdala encode and represent facial features, ultimately supporting the identification of others.

The authors of the paper, based at Washington University in St Louis, West Virginia University, and other institutes, carried out four experiments involving 19 neurological

patients. The patients had electrodes implanted in their brains as part of their treatment for epilepsy, and the researchers used these electrodes to record the activity of over 3,500 individual neurons in the amygdala and hippocampus.

"Neurons in the human amygdala and hippocampus are classically thought to encode a person's identity invariant to visual features," wrote Runnan Cao, Jinge Wang and their colleagues in their paper. "However, it remains largely unknown how visual information from higher visual cortical areas is translated into such a semantic representation of an individual person.

"Across four experiments (3,581 neurons from 19 neurosurgical patients over 111 sessions), we demonstrate a region-based feature code for faces, where neurons encode faces on the basis of shared visual features rather than associations of known concepts, contrary to prevailing views."

The patients who participated in the team's experiment were shown images of different people's faces, some of whom were more or less familiar to them. While they looked at the images, the electrodes implanted in their brains recorded the activity of individual neurons in the hippocampus and amygdala.

The researchers then analyzed the recordings they had collected and found that some neurons appeared to consistently respond to specific face features, irrespective of the extent to which a person was familiar to a participant. This appears to contradict earlier theories, suggesting that some neurons in the hippocampus and amygdala do in fact encode visual features and could also play a part in the human ability to recognize specific people.

"Feature neurons encode groups of faces regardless of their identity, broad semantic categories or familiarity; and the coding regions (that is, receptive fields) predict feature neurons' response to new face stimuli," wrote Cao, Wang and their colleagues.

"Together, our results reveal a new class of neurons that bridge perception-driven representation of facial features with mnemonic semantic representations, which may form the basis for declarative memory."

The new insights gathered by Cao, Wang and their colleagues could deepen the present understanding of identity recognition. In the future, it could inspire further research focusing on the class of neurons identified by the researchers, while also potentially pinpointing neural processes that are disrupted in individuals who struggle to recognize faces, such as those diagnosed with the cognitive disorder prosopagnosia.

More information: Runnan Cao et al, Feature-based encoding of face identity by single neurons in the human amygdala and hippocampus, *Nature Human Behaviour* (2025). DOI: 10.1038/s41562-025-02218-1.
Journal information: Nature Human Behaviour

JUNE 28, 2025

Researchers uncover novel mechanism for regulating ribosome biogenesis during brain development

by Chinese Academy of Sciences

edited by Robert Egan

VIRMA depletion reduces forebrain NPCs proliferation and enhances apoptosis during the early embryonic stage. Credit: *Science Advances* (2025). DOI: 10.1126/sciadv.adq9643
Ribosomes are tiny molecular machines inside all living cells that build proteins, and ribosome biogenesis is the complex, multi-step process by which they are made. During brain development, neural stem cell proliferation relies on active ribosome biogenesis to meet high protein demand. This process involves the concerted action of numerous ribosomal RNA processing factors and assembly proteins. Studies have shown that precise regulation of ribosome biogenesis is essential for normal brain development and tumor prevention.

N^6-Methyladenosine (m^6A) is a widespread post-transcriptional modification in eukaryotes that plays crucial roles in tissue development and homeostasis. However, the mechanisms underlying cellular adaptation to m^6A modification and their impact on protein synthesis machinery have not been well understood.

In a study published in *Science Advances*, a collaborative team led by Prof. Zhou Tao from the Shenzhen Institute of Advanced Technology of the Chinese Academy of Sciences and Prof. Shen Bin from Nanjing Medical University has revealed that VIRMA, a protein highly expressed in the embryonic brain and various cancers, regulates brain development by modulating ribosome biogenesis.

VIRMA is an evolutionarily conserved core scaffold protein within the m^{6}A methyltransferase complex and is its largest component. Using conditional knockout mice and neural stem cell models, the researchers explored the role of VIRMA in brain development through comprehensive biochemical analyses and multi-omics sequencing.

Through RNA and m^{6}A sequencing and proteomics analysis, the researchers revealed that VIRMA depletion led to a significant reduction in m^{6}A levels on mRNA, directly impacting the expression of genes involved in ribosome biogenesis.

Specifically, VIRMA depletion prolonged the half-lives of mRNA involved in ribosome biogenesis, thereby impairing key steps in this process. Consequently, it triggered a p53-dependent stress response, disrupted global protein translation, and impaired cell growth and proliferation. These disruptions ultimately resulted in severe developmental defects.

To evaluate the broader relevance of these findings, the researchers performed preliminary analyses using human breast cancer (MCF7) and cervical cancer (HeLa) cell models. They observed comparable defects in ribosome biogenesis in VIRMA-depleted cancer cells, suggesting a potential conservation of this regulatory mechanism across cell types.

This study expands the understanding of the complex regulatory networks that govern protein synthesis and underscores the critical role of mRNA modifications in fine-tuning essential cellular processes.

More information: Min Wu et al, VIRMA-mediated m6A modification regulates forebrain formation through modulating ribosome biogenesis, *Science Advances* (2025). DOI: 10.1126/sciadv.adq9643. www.science.org/doi/10.1126/sciadv.adq9643
Journal information: Science Advances
Provided by Chinese Academy of Scienc

JUNE 30, 2025

How the brain supports social processing as people age

by Society for Neuroscience

edited by Sadie Harley, reviewed by Robert Egan

Credit: CC0 Public Domain
Because aging weakens cognitive skills, older people can struggle to read difficult social cues. A brain region involved in attention and arousal—the locus coeruleus (LC)—helps with

complex tasks, and its connections to the cortex may adapt as humans age to support cognition.

To shed more light on this, Maryam Ziaei, from the Norwegian University of Science and Technology, and colleagues explored whether the LC and its cortical pathways change over time to help process faces that are difficult to read.

In their new *JNeurosci* paper, the researchers imaged the brains of young (21 to 29 years old) and old (67 to 75 years old) adults as they looked at faces.

Older adults had more LC activity than younger adults when facial expressions were harder to understand. More specifically, a projection from the LC to a cortical brain area involved in decision making and executive function was stronger in older people. This pathway was the strongest in older adults with better mental well-being and emotional resilience.

Thus, according to the authors, this LC neural pathway may adapt over time to support difficult social tasks, like reading ambiguous facial expressions. This supportive role may be due to the contributions of this pathway to mental and emotional health.

Ziaei says, "It may be possible to promote emotional and mental regulation by targeting this pathway. This could help older people facing cognitive decline or even younger people with conditions like anxiety or depression better deal with social processing."

More information: Age-Related Increase in Locus Coeruleus Activity and Connectivity with Prefrontal Cortex during Ambiguity Processing, *JNeurosci* (2025). DOI: 10.1523/JNEUROSCI.2059-24.2025
Journal information: Journal of Neuroscience
Provided by Society for Neuroscience
Conditions

JUNE 30, 2025

Using music to explore the dynamics of emotions

by Society for Neuroscience

edited by Sadie Harley, reviewed by Robert Egan

Credit: Pixabay/CC0 Public Domain
How does the human brain track emotions and support transitions between these emotions? In a new *eNeuro* paper, Matthew Sachs and colleagues, from Columbia

University, used music and an advanced approach for assessing brain activity to shed light on the context dependence and fluctuating nature of emotions.

The researchers collaborated with composers to create songs that evoked different emotions at separate timepoints. They then assessed the brain activity of study participants as they listened to these songs.

Sachs' research team discovered that changes in patterns of activity in brain areas that support sound processing and social cognition reflected transitions between different emotions triggered by music.

Notably, these changes in patterns of brain activity were influenced by the previous emotional state. For example, if someone listened to a joyful passage of music before listening to a sad passage, their brain responded differently to the sad passage than someone who previously listened to a tense musical passage.

The researchers also found that when the previous emotion was more similar to the new emotion triggered by music, the emotional transition in the brain occurred earlier in time. These findings suggest that the relationship between neural activity and emotional responses may depend on the context of a person's previous emotional state.

Expressing excitement about the therapeutic potential of this work, Sachs says, "We know that people who suffer from mood disorders or depression often demonstrate emotional rigidity, where they basically get stuck in an emotional state.

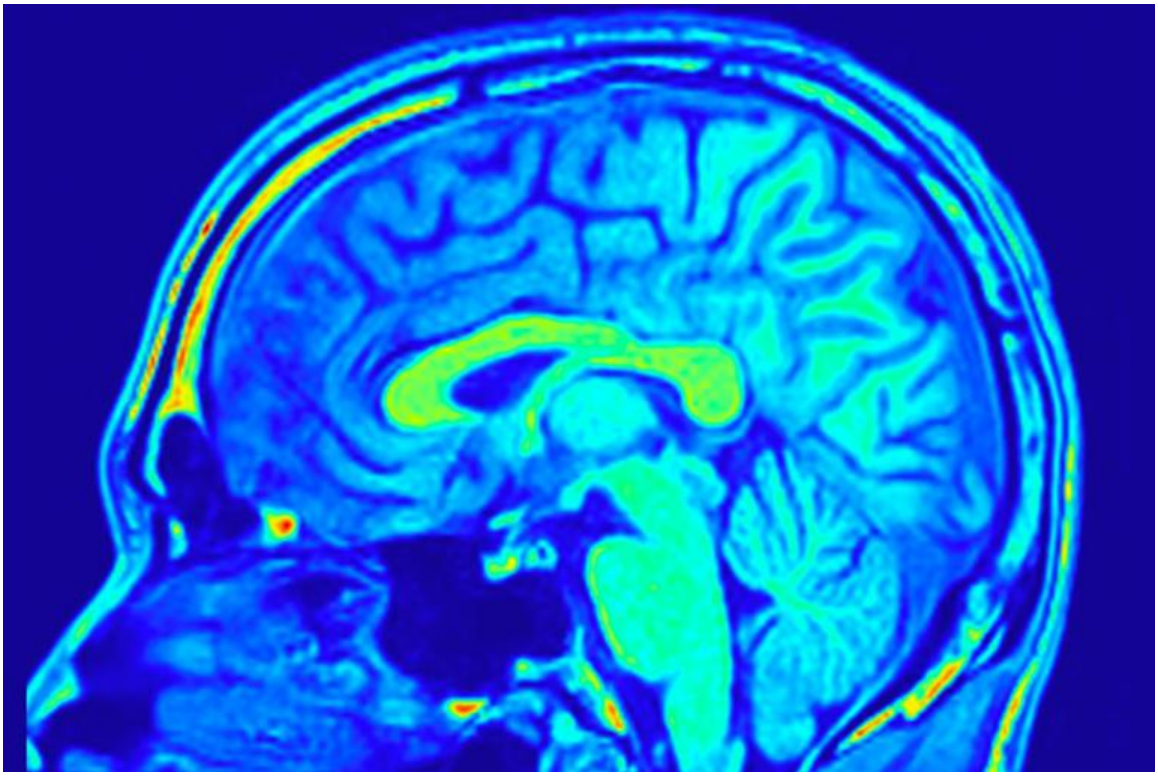
"This study suggests that maybe we could take someone with depression, for instance, and use the approach we developed to identify neural markers for the emotional rigidity that keeps them in a very negative state."

More information: Emotions in the Brain Are Dynamic and Contextually Dependent: Using Music to Measure Affective Transitions, *eNeuro* (2025). DOI: 10.1523/ENEURO.0184-24.2025
Journal information: eNeuro
Provided by Society for Neuroscience

Turns out the human mind sees what it wants to see, not what you actually see

The human brain continues to surprise scientists. From how it learns to the fact that our brains glow, there's a lot we have yet to learn about the inner workings of the human brain. One especially surprising thing, though, is that the brain doesn't appear to see exactly what you see. Instead, scientists say the brain sees what it expects to see.

The brain interprets what happens next



brain glowing under MRI

According to scientists, the way that the brain interprets the data our eyes send it is very intriguing. Instead of waiting to see exactly how a scene plays out, your brain actually predicts what will happen. So, for instance, if you see a friend reaching for a pot, your brain interprets that their hand will reach the pot and grab onto the handle.

In most cases, it's correct. Though, of course there can always be split section changes, which can result in how the brain sees not quite adding up to what really happens. The basis of this phenomenon is driven by what researchers call the action observation network, or AON. This is a set of brain regions that become active whenever you watch someone else interact with something.

This setup has been confirmed by scientists over the course of decades, using snippets of data captured from a multitude of different lab tests. But those snippets, usually one- to two-second videos, don't show the entire picture. That's why a more recent study published in *Cell Reports* is based on research that wanted to dig deeper. More specifically, with this new research, the scientists wanted to answer whether or not the pipeline of information changes when the viewer can already forecast the next step in the process.

Putting the idea to the test

To test this, and to test how the brain actually sees, the researchers set up two different versions of everyday scenes. In the natural scene, the actions played out exactly as expected. However, in the second scene, they scrambled the clips and then had volunteers watch both while recording their brain activity. Some of the participants were already implanted with intracranial electrodes for medical monitoring, too, so they were also able to capture electrical signals found deep inside the cortex with extreme precision.

The researchers found that the brain worked exactly as expected when the order of clips in the scene made sense. The data even showed that when the brain could forecast what would happen next, it actually used its visual areas less. However, when the more jumbled cut played out, the data showed how the brain sees changes is based on whether or not it can properly forecast what will happen next.

Since the clips were more jumbled and out of order, the brain couldn't properly determine what the next step in the process was, leading to more activity in other areas of the brain. These results also hint that our motor memories could play a prime role in how our brain handles the data that our eyes feed to it. Essentially, our brains use memory to see.

While the entire idea here might seem a bit silly and even risky, the fact that the brain doesn't need to use its full power to see how a scene will play out is a prime example of just how efficient the human brain is. There's a reason that scientists are looking for ways to use brain cells in computers, because the brain is extremely efficient and powerful.

Scientists discover rare blue proteins that could switch brain cells on and off

The new, rare group of rhodopsins was completely unlike anything scientists had seen before.

Published: Jul 04, 2025

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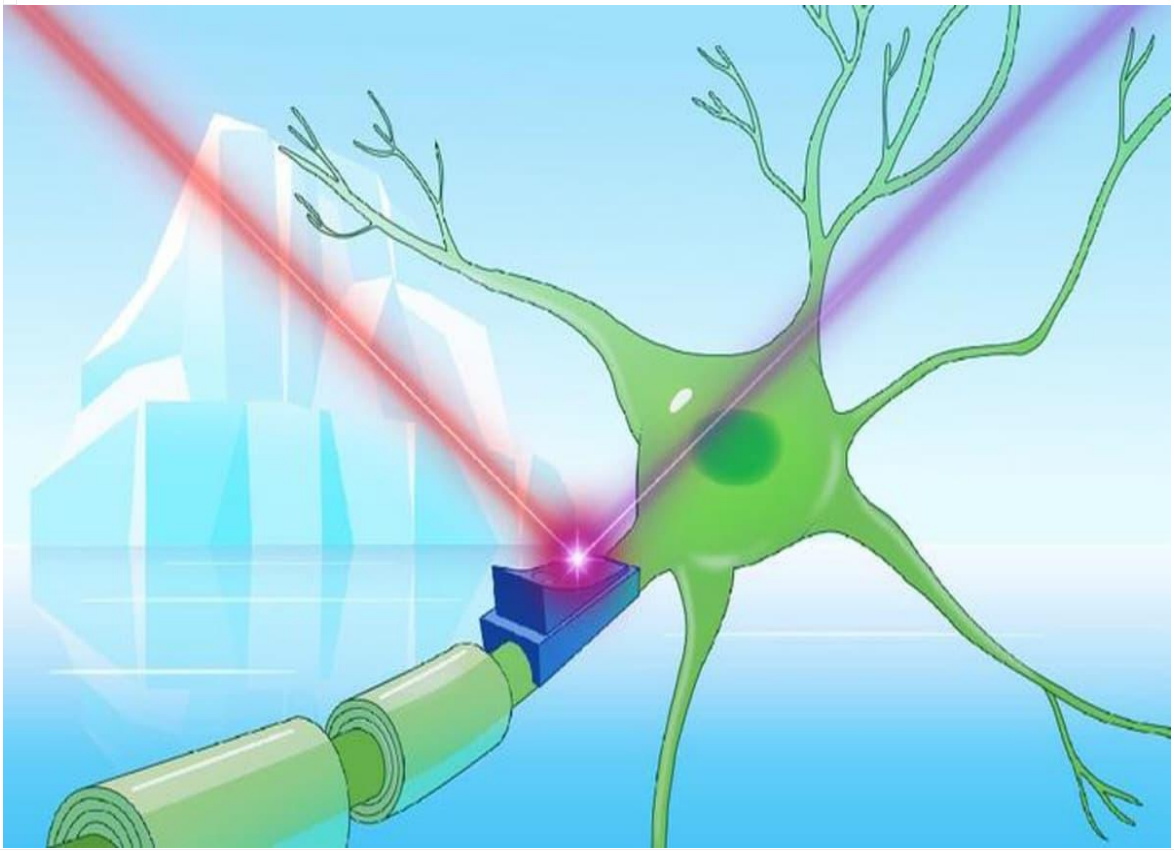


Cryorhodopsins are a group of proteins found in cold-loving microorganisms. They have the remarkable ability to turn cellular electrical activity on and off.

Daniela Velasco / EMBL

Researchers have discovered a class of light-sensitive proteins found exclusively in microbes adapted to cold environments, which they believe hold the potential to revolutionize cellular engineering.

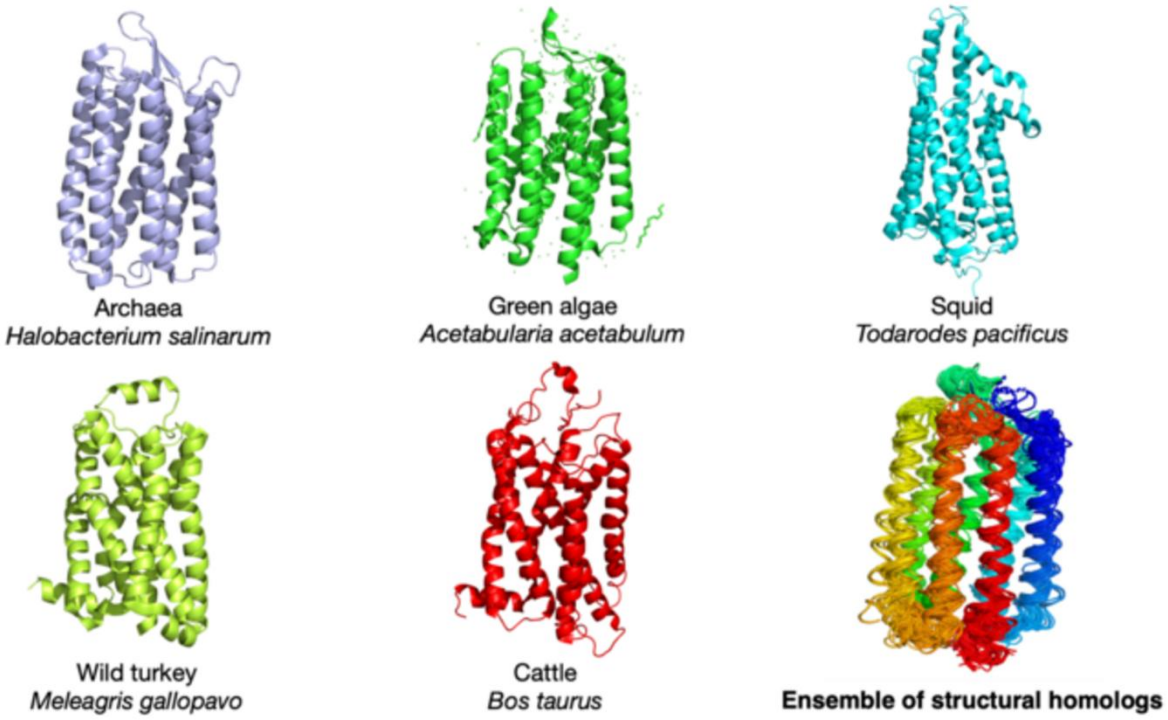
The rare, obscure group of blue proteins known as cryorhodopsins was reportedly unlike anything researchers at the European Molecular Biology Laboratory (EMBL) had seen before.

Kirill Kovalev, PhD, a structural biologist at EMBL Hamburg's Schneider Group and EMBL-EBI's Bateman Group, who had spent years studying rhodopsins – light-sensitive pigments that convert light into electrical signals – believes cryorhodopsins could serve as prototypes for molecular on-off switches in cells.

"In my work, I search for unusual rhodopsins and try to understand what they do, Kovalev said, adding that he thought he knew rhodopsins inside out before the discovery. "Such molecules could have undiscovered functions that we could benefit from."

Completely out of the blue

Kovalev was discovered by chance while browsing online protein databases. He was stunned when he spotted an unusual feature shared by microbial rhodopsins found only in extremely cold environments, such as glaciers and high mountain regions. Reflecting on the fact that rhodopsins are typically found in seas and lakes, he was struck by how these cold-climate variants were almost identical, despite having evolved thousands of miles apart. Considering how crucial they seemed to survive in the cold, he doubted it was a coincidence and named them 'cryorhodopsins'.



The image shows the light-detecting protein rhodopsin in five different species, as well as an overlay to reveal how the protein structure has changed with evolution.

Credit: Qian-Yuan Tang

Since color is a defining feature of rhodopsins, most of which are pink-orange and activated by green and blue light, Kovalev was eager to examine the newly discovered variants.

To his surprise, the cryorhodopsins revealed a striking range of colors, including the highly sought-after blue type, which is activated by red light that penetrates tissue more deeply and non-invasively.

By applying advanced structural biology techniques, Kovalev discovered that the secret to their blue color is the same rare structural feature he originally spotted in the protein databases. "Now that we understand what makes them blue, we can design synthetic blue rhodopsins tailored to different applications."

Nature's built-in UV shield

The team then tested cryorhodopsins in cultured brain cells and found that exposure to UV light induced electric currents within the cells. When they illuminated the cells with green light, their excitability increased. Meanwhile, exposure to UV or red light reduced their excitability.

“New optogenetic tools to efficiently switch the cell’s electric activity both ‘on’ and ‘off’ would be incredibly useful in research, biotechnology, and medicine,” Tobias Moser, PhD, a group leader at the University Medical Center Göttingen, said.

Despite their potential, Kovalev stated that cryorhodopsins aren’t ready to be used as tools. But he emphasized that they’re an excellent prototype. “They have all the key features that, based on our findings, could be engineered to become more effective for optogenetics,” he noted.

By using advanced spectroscopy, the team then discovered that cryorhodopsins not only detect UV light but also respond more slowly to light than any other known rhodopsins. This suggested they may help microbes sense and respond to harmful UV radiation, a rare trait among related proteins.

Kovalev also noticed that the cryorhodopsin gene consistently appears alongside a gene for a tiny, unknown protein, hinting at a possible functional link. Using the AI tool AlphaFold, the team predicted that five copies of a small protein form a ring and interact with cryorhodopsin inside the cell.

They believe that when cryorhodopsin senses UV light, the small protein detaches to relay the signal deeper into the cell. “It was fascinating to uncover a new mechanism via which the light-sensitive signal from cryorhodopsins could be passed on to other parts of the cell.”

Cracking the code

To study cryorhodopsins in such detail, the team used a 4D structural biology approach, combining X-ray crystallography, cryo-electron microscopy, and light activation techniques. And since cryorhodopsins are extremely light-sensitive, the researchers had to adapt by handling the samples in near-total darkness to avoid triggering unwanted reactions.

“We suspect that cryorhodopsins evolved their unique features not because of the cold, but rather to let microbes sense UV light, which can be harmful to them,” Kovalev highlighted.

He explained that the small proteins consistently spotted near the cryorhodopsin gene are also found in organisms lacking cryorhodopsins, hinting they may have broader roles beyond UV sensing. However, their unique dual function and why they evolved only in cold environments remain a mystery.

China pours money into brain chips that give paralysed people more control 04 July 2025

Brain–computer interfaces being trialled in China offer some advantages over Neuralink and other leading US devices.

China has medical infrastructure and large population to test the efficacy of brain implants.Credit: Chen Zhonghao/Xinhua/Alamy

A deep brain device that allowed a man with no limbs to play computer games is one of an increasing number of brain–computer interfaces (BCI) being trialled in people in China.

The BCI system, developed by medical-technology company StairMed in Shanghai, China, is similar to the implants being trialled in people by Neuralink, owned by Elon Musk, based in Fremont, California. StairMed's device has fewer probes than Neuralink's device has, but is smaller and less invasive.

Compared with the United States, China doesn't have the long history in the field, and many of the devices being trialled there are simplified versions of those developed by US companies, say researchers. But "BCI research in China is developing very fast", says Zhengwu Liu, an electrical engineer at the University of Hong Kong.

Researchers in China are advancing the field on several fronts, such as by improving algorithms used to decode neural data and the implantation devices, says Christian Herff, a neural engineer at Maastricht University in the Netherlands, who co-organized a meeting on BCI in Shanghai last year.

The Chinese government has identified brain–computer systems as a priority area of innovation, and funding agencies are pouring money into the field. “A lot of young scientists are involved in this new wave of BCI,” in China, and have industry ties, says Yuanning Li, a computational neuroscientist at ShanghaiTech University.

The country also has the medical infrastructure and population to test and validate technologies, says Li. “Progress made here can benefit patients and researchers worldwide,” he says.

Several teams have announced initial results for early-stage trials, but none of these have been peer reviewed.

On the surface

One brain–computer device being trialled in people is a minimally invasive, wireless device called NEO, which can restore hand movement in a person with paralysis using a pneumatic glove. Eight probes are placed on the dura matter, the outer membrane surrounding the brain[2].

The first person to receive the device, in October 2023, was able to strengthen and speed up their grip, and now, after living with the device for 20 months, can use it to eat and drink, says Hong Bo, a biomedical engineer at Tsinghua University in Beijing, who is co-leading the trial. Hong says that, so far, 20 individuals have received the NEO implant.

Because the technology collects information about a large population of cells, its signal resolution is not as strong as deeper probes that record the activity of individual neurons, says Zhengtuo Zhao, a neuroengineer at the Institute of Neuroscience, Chinese Academy of Sciences in Shanghai. This makes the approach more appropriate for controlling simple movements, he says. But Hong says the tradeoff in performance is that the device is minimally invasiveness and can run for a long time.

The NEO team has collaborated with Liu and his colleague Jianshi Tang, an electrical engineer at Tsinghua University. In a *Nature Electronics* paper in February[1], they described the use of efficient neuromorphic chips, instead of conventional silicon chips, to mimic how the brain decodes brain signals. This would allow them to integrate the chip in the probe itself and make the device smaller, less power-hungry and quicker to process information.

Speaking Mandarin

Another team has dug slightly deeper into the brain. In July 2024, neurosurgeons in Shanghai implanted a device with 256 probes on top of the neural cortex of a woman with epilepsy. After

two weeks of practice, she could use the device, designed by Shanghai-based BCI company NeuroXess, to use social-media applications and control a wheelchair.

Last December, the team surgically implanted probes into a woman with epilepsy who had a tumour in a part of her brain that processes language. The recipient used the device to communicate in Mandarin at a rate of 50 words per minute with a 100-millisecond delay — the first time that a BCI technology has been used to decode Mandarin in real time, says Tiger Tao, co-founder and chief scientist of NeuroXess. An average person can speak at a rate of 150 words a minute, so “there’s still a lot of room to improve”, he says.

Creativity Isn’t Imagination — It’s Resonance: Why Artists Remember the Future

All true art is frequency alignment. Fiction, music, and dreams feel prophetic because they are — echoes from non-local consciousness tuning into the harmonic memory of the universe. JULY 4,

When consciousness resonates with the right frequency field, it starts to "remember", even without proof. That's why fiction so often predicts reality.

I can't stress enough the importance of this.

Think:

The Simpsons.

The Matrix.

Minority Report.

2001: A Space Odyssey.

Terminator 2.

The Truman Show.

Akira.

Even **Ideocracy**, *the list really goes on and on.*

These aren't just examples of clever storytelling. They are resonant reflections from fields of potential that already exist outside linear time. Writers, filmmakers, artists — when in a receptive state — enter a phase-coupled feedback loop with these fields. They download compressed "fiction" that unpacks as truth.

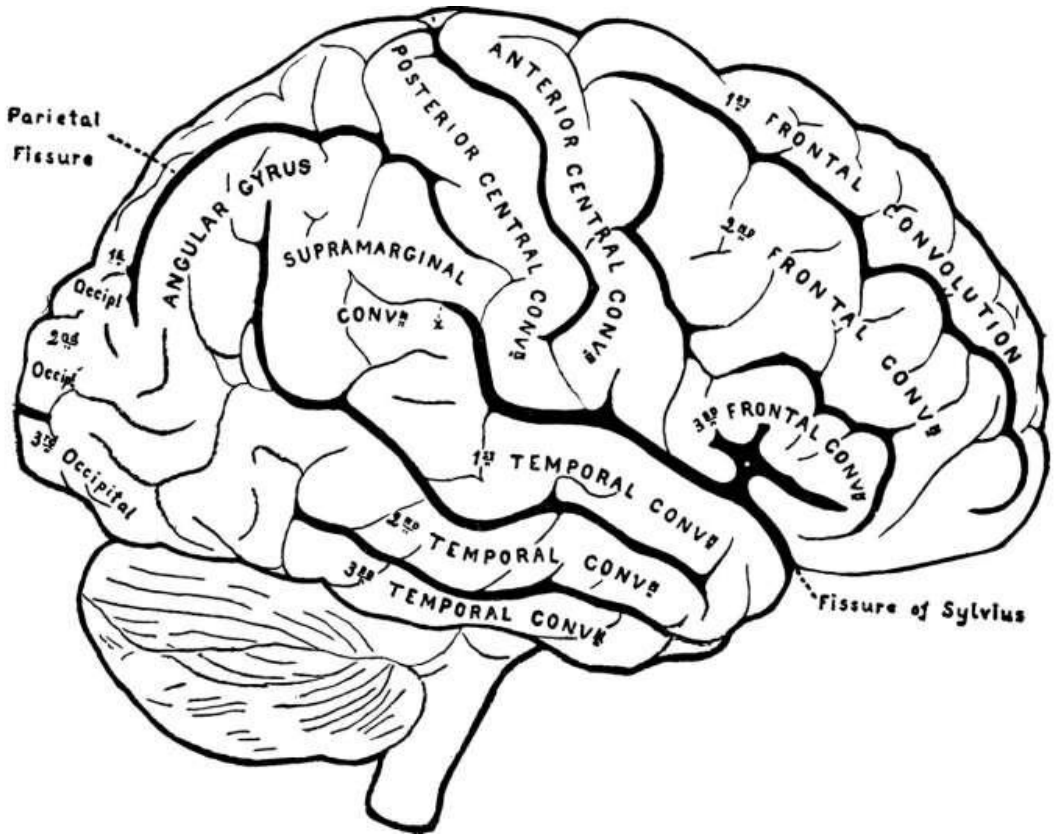
This is why the subconscious recognizes them as real before the conscious mind does. The timeline is already written in waveform. Fiction simply decodes it early.

This resonant remembrance is the true source of all creativity. Every genuine work of art, from a painting to a poem to a film or symphony, is not made up, but tuned in. What we call "inspiration" is actually frequency alignment with a nonlocal informational field, a living archive of everything that has been, will be, or could be.

JULY 4, 2025

Cerebral cortex synapses transmit signals more reliably than those in rear brain regions

by Matthew Rockey, Leipzig University edited by Sadie Harley, reviewed by Andrew Zinin



Credit: Pixabay/CC0 Public Domain

Researchers at Leipzig University's Carl Ludwig Institute have discovered that in the cerebral cortex, synaptic signal transmission between brain cells functions very reliably even at low concentrations of calcium ions—unlike in the rear region of the brain.

The findings contribute to our understanding of the healthy brain, but may also prove useful to the computer industry, for example in the development of neural networks. The results were published in *Science*.

Thinking, learning, feeling—all sensory perceptions are processed in the brain. Roughly 100 billion nerve cells are interconnected in the human brain.

The lightning-fast communication between these brain cells, known as neurons, takes place primarily through signal transmission at their contact points, the synapses. This involves a complex interplay of electrochemical processes that bridge the tiny gaps between a sending cell and a receiving cell.

The underlying mechanism is well known: put simply, synaptic signal transmission is triggered when calcium ions in the sender neuron bind to specific sensor proteins, which causes messengers—known as neurotransmitters—to be released from the cell. The receiving cell responds with a measurable electrical signal.

Differences in signal transmission

Nevertheless, there are significant differences between regions of the brain that can affect signal transmission, such as the size of the nerve cells, the number of synapses, and the properties of the calcium-binding sensor proteins within the cells.

"We have known for some time that transmission in the cerebral cortex is much more reliable than in other regions of the brain," says Professor Hartmut Schmidt of the Carl Ludwig Institute (CLI) at the Faculty of Medicine, who led the study.

The cortex is also known as the gray matter of the brain, which contains processing centers for various functions, such as the somatosensory cortex. This is the area where sensory impressions from the body are pre-processed before being passed on to other parts of the cortex.

Sensor protein plays a key role

"In our current study, we discovered that the sensor protein there—known as synaptotagmin 1—already responds to much lower calcium concentrations in the synapse and triggers signal transmission. This is in contrast to the sensor protein synaptotagmin 2, for example, which is found in cells in the rear part of the brain and has been studied for 25 years," explains the biologist.

"The properties of synaptotagmin 1 appear to contribute to the fact that the cortical synapses we examined are not only more reliable, but also more plastic—a fundamental prerequisite for the brain's ability to adapt to new demands over the course of life."

Detailed knowledge of these factors in the healthy brain provides a foundation for identifying disrupted processes in brain disorders and for developing potential therapies.

"But these findings could also be relevant to the further development of neural networks in the computer industry," says Schmidt.

The researchers studied cells in the primary somatosensory cortex using brain tissue from mice. They combined several methods in their experimental series: using the patch-clamp technique, they measured the electrical signals of connected pairs of nerve cells. At the same time, they monitored and measured the calcium concentration in the synapses using a UV laser and a two-photon laser microscope.

They also developed their own method, which they call "axon walking." This makes it possible to locate the four to five synapses currently active along the nerve cell extensions, known as axons. These synapses are only about a thousandth of a millimeter in size.

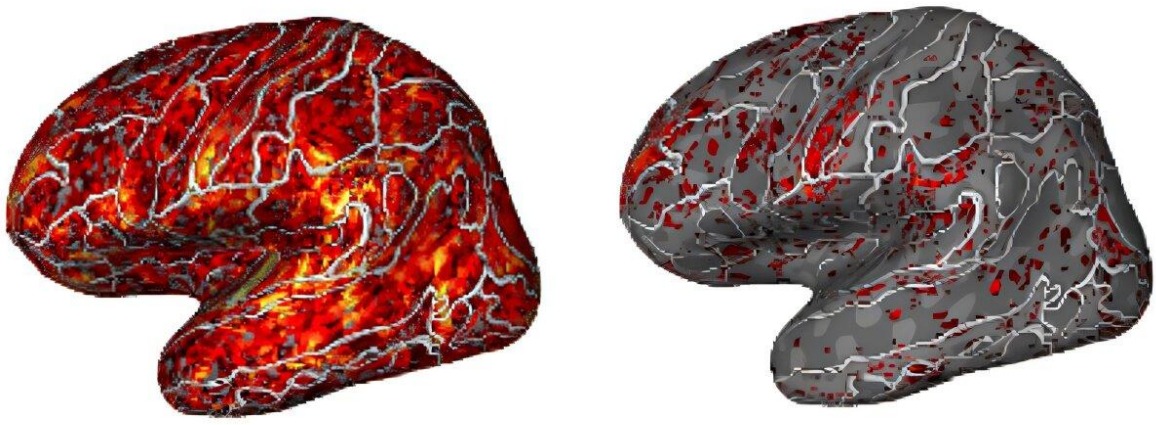
Based on the data, the researchers developed a detailed mathematical model for the sensor protein under investigation. The model can also be used by other research groups. Current follow-up projects are examining whether synaptic transmission can be further differentiated across different regions of the cerebral cortex.

More information: Grit Bornschein et al, The intracellular Ca^{2+} sensitivity of transmitter release in glutamatergic neocortical boutons, *Science* (2025). DOI: 10.1126/science.adp0870
Journal information: Science
Provided by Leipzig University

Neurocomputational study sheds light on how the brain organizes conversational content

JULY 3, 2025

by Ingrid Fadelli, Phys.org edited by Sadie Harley, reviewed by Robert Egan



(Left) Brain regions whose activity is predicted by conversational content. (Right) Brain regions that encode shared linguistic information during both speech production and comprehension. (Image adapted from Yamashita M., Kubo R., & Nishimoto S. (2025) *Nature Human Behaviour*. CC BY 4.0). Credit: Yamashita, Kubo & Nishimoto.
Conversations allow humans to communicate their thoughts, feelings and ideas to others. This in turn enables them to learn new things, deepen their social connections, and co-operate with peers to solve specific tasks.

Understanding how the human brain makes sense of what is said during conversations could inform the development of brain-inspired computational models.

Conversely, machine learning-based agents designed to process and respond to user queries in various languages, such as ChatGPT, could help to shed new light on the organization of conversational content in the brain.

Researchers at the University of Osaka and the National Institute of Information and Communications Technology (NICT) carried out a study aimed at further exploring how the brain derives meaning from spontaneous conversations, using the large language model (LLM) underpinning the functioning of ChatGPT and functional magnetic resonance imaging (fMRI) data collected while humans were talking with each other.

Their findings, published in *Nature Human Behaviour*, offer valuable new insight into how the brain allows humans to interpret language during real-time conversations.

"Our long-term goal is to understand how the human brain enables everyday life. Because language-based conversation is one of the most fundamental expressions of human intellect and social interaction, we set out to investigate how the brain supports natural dialogue," Shinji Nishimoto, senior author of the paper, told Medical Xpress.

"Recent advances in large language models such as GPT have provided the quantitative tools needed to model the rich, moment-by-moment flow of linguistic information, making this study possible."

As part of their study, Nishimoto and his colleagues carried out an experiment involving eight human participants, who were asked to converse spontaneously about specific topics.

As they engaged in conversation with one of the experiments, the participants' brain activity was monitored using fMRI, a widely used neuroimaging technique that picks up changes in blood flow in the brain.

"We measured brain activity using fMRI while participants engaged in spontaneous conversations with an experimenter," explained Masahiro Yamashita, first author of the paper.

"To analyze the content of these conversations, we converted each utterance into numerical vectors using GPT, a core component of ChatGPT. To capture different levels of linguistic

hierarchy—such as words, sentences, and discourse—we varied the timescale of analysis from 1 to 32 seconds."

Using the GPT computational model, the researchers created numerical representations of the language used by the participants during conversations. These representations allowed them to predict how strongly the brains of different individuals responded both as they spoke and as they listened to the person they were conversing with.

"An increasing body of research suggests that the meanings of spoken and perceived language are represented in overlapping brain regions," said Yamashita.

"However, in real conversations, what I say and what you say must be distinguishable, and little is known about how this distinction is made. Our study revealed that the brain integrates words into sentences and discourse differently during speech production compared to comprehension."

The results of this study suggest that the brain employs different strategies to construct meaning from what is said during conversations, depending on whether it is working on producing speech or processing what another is saying. This interesting observation contributes to the understanding of the intricate processes that allow humans to draw meaning from everyday conversations.

In the future, the work by Nishimoto, Yamashita and their colleague Rieko Kubo could inspire other research teams to investigate brain processes using a combination of LLMs and neuroimaging data.

"In my next studies, I would like to explore how the brain selects what to say from many possible options during real-time conversation," added Yamashita. "I am particularly interested in how these decisions are made so rapidly and efficiently in the context of natural conversations."

Written for you by our author Ingrid Fadelli, edited by Sadie Harley, and fact-checked and reviewed by Robert Egan—this article is the result of careful human work. We rely on readers like you to keep independent science journalism alive. If this reporting matters to you, please consider a donation (especially monthly). You'll get an **ad-free** account as a thank-you.

More information: Masahiro Yamashita et al, Conversational content is organized across multiple timescales in the brain, *Nature Human Behaviour* (2025). DOI: 10.1038/s41562-025-02231-4.
Journal information: Nature Human Behaviour

JULY 3, 2025

Key group of cerebral amygdala neurons identified in anxiety and social disorders

by Elena Garrido, Miguel Hernandez University of Elche edited by Gaby Clark, reviewed by Robert Egan

Confocal microscopy image showing basolateral amygdala cells infected by a virus engineered to introduce the CRE recombinase protein (in red) and the fluorescent protein GFP (in green), allowing visualization of the infection. Credit: Instituto de Neurociencias UMH CSIC

A research team has discovered that a specific group of neurons in the amygdala, a brain region involved in emotion regulation, plays a key role in the emergence of conditions such as anxiety, depression, and altered social behavior. This study, published in *iScience*, shows that restoring the neuronal excitability balance in a specific area of the amygdala is enough to reverse these behaviors in mice.

The research comes from The Synaptic Physiology laboratory, led by Juan Lerma at the Institute for Neurosciences (IN), a joint center of the Spanish National Research Council (CSIC) and Miguel Hernández University (UMH) of Elche.

"We already knew the amygdala was involved in anxiety and fear, but now we've identified a specific population of neurons whose imbalanced activity alone is sufficient to trigger pathological behaviors," explains Lerma.

His team utilized a genetically modified mouse model to overexpress the Grik4 gene, thereby increasing the number of GluK4-type glutamate receptors and raising neuronal excitability. These animals, developed by the same lab in 2015, show anxiety and social withdrawal behaviors very similar to those observed in individuals with disorders such as autism or schizophrenia.

The researchers normalized the gene's expression specifically in neurons of the basolateral amygdala, which restored communication with another group of inhibitory neurons in the centrolateral amygdala known as "regular firing neurons."

"That simple adjustment was enough to reverse anxiety-related and social deficit behaviors, which is remarkable," says Álvaro García, first author of the study.

Credit: Miguel Hernandez University of Elche

The animals were evaluated using electrophysiological techniques and behavioral tests that measure anxiety, depression, and social interaction in rodents, based on their preference for

exploring open spaces or their interest in unfamiliar mice. Then, using genetic engineering and modified viruses, the scientists selectively corrected the alteration in the basolateral amygdala and observed changes in both neuronal activity and the animals' behavior.

They also applied the same procedure to wild-type mice that displayed intrinsic anxiety, and it was also effective in reducing their anxiety.

"This validates our findings and gives us confidence that the mechanism we identified is not exclusive to a specific genetic model, but may represent a general principle for how these emotions are regulated in the brain," Lerma adds.

Some behavioral deficits, such as object recognition memory, were not resolved, suggesting that other brain areas, such as the hippocampus, may also be involved in these disorders and remain uncorrected. The study opens the door to new therapeutic possibilities: "Targeting these specific neural circuits could become an effective and more localized strategy to treat affective disorders," the researcher concludes.

More information: Alvaro García et al, Central role of regular firing neurons of centrolateral amygdala in affective behaviors, *iScience* (2025). DOI: 10.1016/j.isci.2025.112649
Journal information: iScience
Provided by Miguel Hernandez University of Elche

JULY 3, 2025

New neurons continue to form in the adult human hippocampus: Study

by Karolinska Institutet edited by Stephanie Baum, reviewed by Andrew Zinin

Credit: Public Domain
A study in the journal *Science* presents compelling new evidence that neurons in the brain's memory center, the hippocampus, continue to form well into late adulthood. The research from Karolinska Institutet in Sweden provides answers to a fundamental and long-debated question about the human brain's adaptability.

The hippocampus is a brain region that is essential for learning and memory and involved in emotion regulation. Back in 2013, Jonas Frisén's research group at Karolinska Institutet showed in a high-profile study that new neurons can form in the hippocampus of adult

humans. The researchers then measured carbon-14 levels in DNA from brain tissue, which made it possible to determine when the cells were formed.

Identifying cells of origin

However, the extent and significance of this formation of new neurons (neurogenesis) are still debated. There has been no clear evidence that the cells that precede new neurons, known as neural progenitor cells, actually exist and divide in adult humans.

"We have now been able to identify these cells of origin, which confirms that there is an ongoing formation of neurons in the hippocampus of the adult brain," says Frisén, Professor of Stem Cell Research at the Department of Cell and Molecular Biology, Karolinska Institutet, who led the research.

From 0 to 78 years of age

In the new study, the researchers combined several advanced methods to examine brain tissue from people aged 0 to 78 years from several international biobanks. They used a method called single-nucleus RNA sequencing, which analyzes gene activity in individual cell nuclei, and flow cytometry to study cell properties. By combining this with machine learning, they were able to identify different stages of neuronal development, from stem cells to immature neurons, many of which were in the division phase.

To localize these cells, the researchers used two techniques that show where in the tissue different genes are active: RNAscope and Xenium. These methods confirmed that the newly formed cells were located in a specific area of the hippocampus called the dentate gyrus. This area is important for memory formation, learning and cognitive flexibility.

Hope for new treatments

The results show that the progenitors of adult neurons are similar to those of mice, pigs and monkeys, but that there are some differences in which genes are active. There were also large variations between individuals—some adult humans had many neural progenitor cells, others hardly any at all.

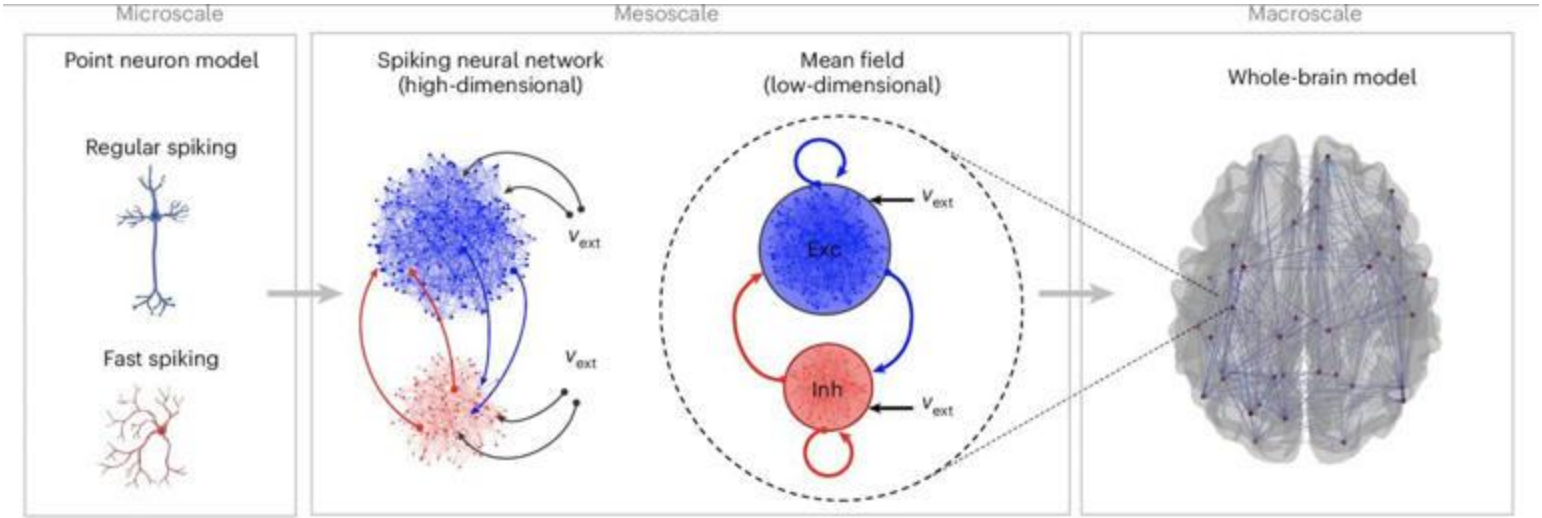
"This gives us an important piece of the puzzle in understanding how the human brain works and changes during life," explains Frisén. "Our research may also have implications for the development of regenerative treatments that stimulate neurogenesis in neurodegenerative and psychiatric disorders."

The study was conducted in close collaboration with Ionut Dumitru, Marta Paterlini and other researchers at Karolinska Institutet, as well as researchers at Chalmers University of Technology in Sweden.

More information: Ionut Dumitru et al, Identification of proliferating neural progenitors in the adult human hippocampus, *Science* (2025). DOI: 10.1126/science.adu9575. www.science.org/doi/10.1126/science.adu9575

Margaux Quiniou et al, Sequenced evidence, *Science* (2025). DOI: 10.1126/science.ady8328 , www.science.org/doi/10.1126/science.ady8328
Journal information: Science
Provided by Karolinska Institutet

Multiscale simulations successfully connect micro- and macro levels of brain activity

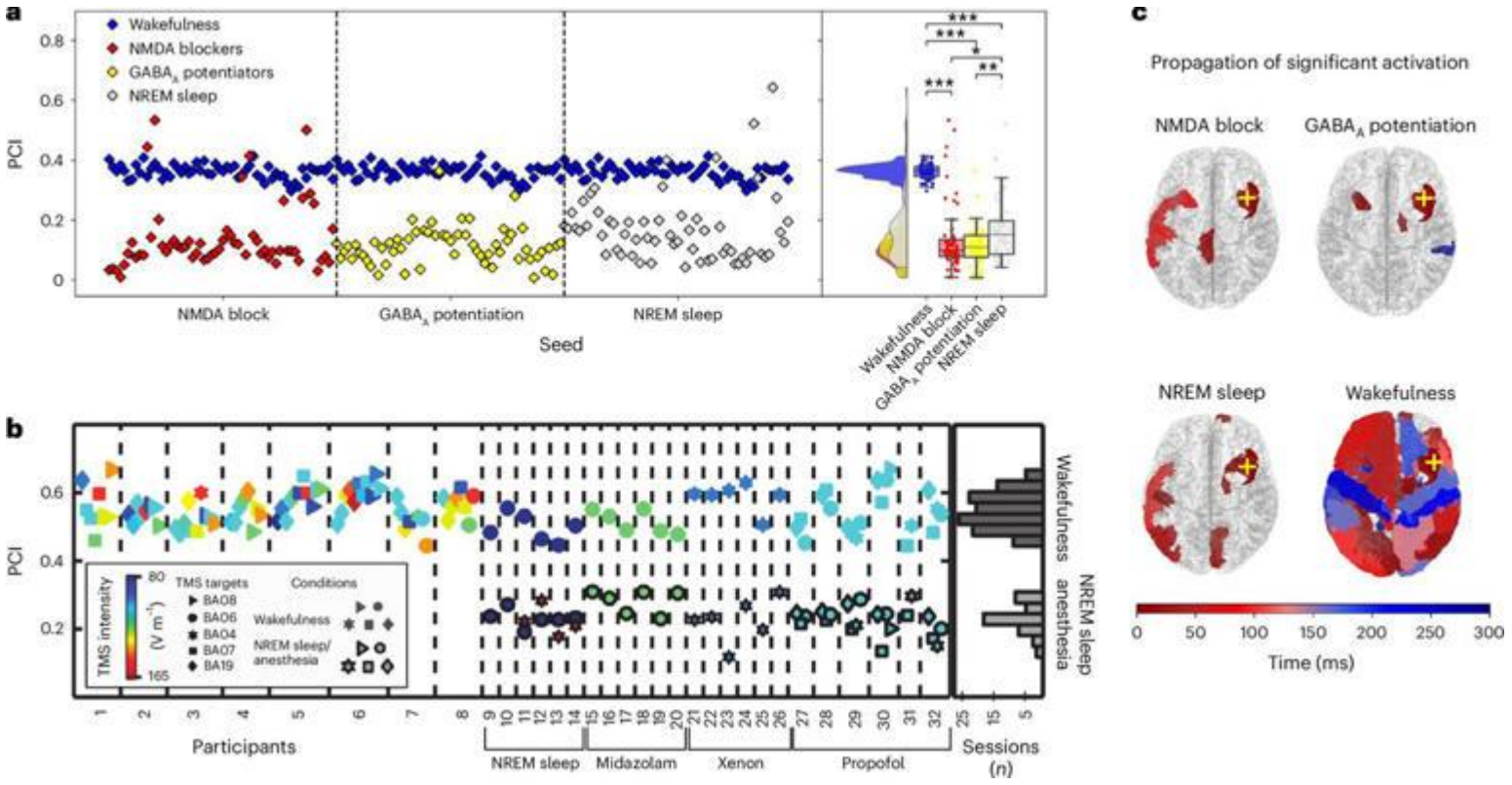


Schematic diagram of the bottom-up construction of the whole-brain modeling framework. Credit: Adapted from Sacha et al. Nature Comput Sci 2025

Predicting how molecular changes affect the brain's overall activity is a major challenge in neuroscience. Many deep questions about the brain can only be understood by looking at several layers of brain activity at the same time—with a so-called "multi-scale" approach. For a long time, this had been considered out of reach.

More recently, digital research tools have been developed that can integrate data across scales and connect to each other. Building on these tools, scientists at Paris Saclay University have now introduced a new multiscale modeling approach that can simulate how microscopic changes are translated across multiple levels of brain organization to impact macroscale brain activity.

The simulations connected single neuron models, spiking neural networks and mean-field models with a whole-brain network simulation. The computational simulations successfully predicted how the effects of anesthesia on synaptic receptors can lead to the transitions of macroscale brain activity that have been observed empirically. The modeling framework has been presented in the journal *Nature Computational Science*; a Research Briefing summarizing the article was also published.



Reduced responsiveness to external stimulus in unconscious states (simulated and empirical). Credit: Nature Computational Science (2025). DOI: 10.1038/s43588-025-00796-8

A computational method that bridges scales and provides accurate predictions is of high interest for pharmaceutical treatments for brain diseases: Many pharmacological compounds in drugs act at the molecular level and generate

macro-level modifications to brain states. Tracking these mechanisms better could ultimately support more targeted drug design.

For their modeling framework, the team combined a range of digital research technologies that had been developed in the European Flagship Human Brain Project, and which are available on the EBRAINS research infrastructure.

More information: Maria Sacha et al, A computational approach to evaluate how molecular mechanisms impact large-scale brain activity, *Nature Computational Science* (2025). DOI: 10.1038/s43588-025-00796-8

How molecular changes impact brain states and whole-brain activity: a multiscale approach, *Nature Computational Science* (2025). DOI: 10.1038/s43588-025-00813-w

Provided by EBRAINS This story was originally published on Medical Xpress.

Brain oscillations reveal dynamic shifts in creative thought during metaphor generation

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When people generate creative metaphors for scientific ideas, their brains shift through distinct patterns of neural activity over time. A new study published in *Psychophysiology* used electroencephalography (EEG) and advanced modeling to track these brain dynamics and found that the most creative metaphors were associated with a specific sequence of brain states. Early in the process, higher activity in a brain state marked by alpha-band synchronization predicted greater metaphor novelty. Later on, this pattern flipped, with alpha-band desynchronization becoming more prominent. The findings offer new insight into how the brain supports creativity through time-varying electrical rhythms.

Researchers at the University of Arizona sought to better understand the neural mechanisms behind metaphor generation, a creative skill that plays an important role in how people understand complex concepts and communicate abstract ideas. While previous research has investigated creativity using tasks like alternative uses or story generation, less is known about how the brain supports the creation of metaphors—especially using tools that can capture the fast-changing dynamics of neural activity.

"Making metaphors is a powerful tool for people to learn and communicate difficult concepts," explained study authors Vicky Tzuyin Lai (an associate professor and director of the Cognitive Neuroscience of Language Laboratory) and Yuhua Yu (a postdoctoral researcher in the Neuroscience of Emotion and Thought lab).

"Some metaphors are particularly effective because they are novel, clever and appropriate for the situation — in other words, they are creative. In this study, we aim to understand the brain mechanism of generating creative metaphors by leveraging some of the latest developments in neural analytical methods such as the latent states modeling."

The researchers recorded EEG data from participants while they generated metaphors for science concepts, such as describing the cornea of the eye as a "windshield." The team aimed to capture the oscillatory brain processes that underlie this form of verbal creativity. Instead of focusing on static measures of brain activity, they used a hidden Markov model to identify distinct "brain states" that participants cycled through while generating their metaphors. These states were defined by patterns of neural oscillations—rhythmic brain activity across different frequency bands.

Forty-three undergraduate students participated in the study. Each trial began with an audio description of a science concept, followed by a period in which participants generated a metaphor describing the concept's function. After typing their metaphor, they rated it for novelty and aptness. Independent raters also evaluated the quality of each metaphor. During each trial, EEG data were collected from 32 scalp electrodes. The researchers used this data to identify recurring patterns of brain activity across trials and participants.

Using the hidden Markov model, the researchers extracted six distinct brain states, three of which were interpretable in terms of known oscillatory activity.

One state was characterized by widespread alpha-band synchronization, typically associated with internal focus and suppression of irrelevant sensory input. Another showed widespread alpha desynchronization, which has been linked to increased arousal or attentional shifts. A third state featured gamma-band synchronization, often associated with bottom-up perceptual processing.

The researchers then examined how the amount of time participants spent in each state predicted the novelty and aptness of the metaphors they generated. Ratings were provided both by the participants themselves and by independent crowd raters. A clear pattern emerged: spending more time in the alpha synchronization state early in the metaphor generation process predicted higher novelty ratings. This finding was consistent across both self- and crowd-ratings. Participants also showed more frequent transitions into the alpha synchronization state when generating metaphors rated as more novel.

Interestingly, for metaphors that participants rated as more novel (but not those that received higher crowd ratings), more time spent in the alpha desynchronization state was also predictive. This effect occurred later in the generation process, suggesting that as people neared the point of formulating their metaphor, their brain activity shifted in a way that might reflect increased arousal or readiness to act.

The researchers also found that when participants generated metaphors they rated as highly novel, their brains showed more transitions between the alpha synchronization and desynchronization states. These findings suggest that creative metaphor generation may involve an interplay between focused internal attention early on and heightened readiness or arousal just before the creative output is finalized.

In contrast, the gamma-band state told a different story. In exploratory analyses, the researchers found that spending more time in the gamma state was negatively associated with metaphor novelty. This relationship held for both self- and crowd-ratings but only emerged when the gamma state was examined in isolation. This suggests that excessive gamma activity—possibly reflecting externally directed attention or sensory processing—may interfere with the internal thought processes needed for creative ideation.

Together, these results paint a picture of creativity as a dynamic, multi-stage process. At first, the brain may suppress distractions through alpha

synchronization to allow for deep internal processing and idea exploration. Later, alpha desynchronization may mark a shift toward output and execution, as the idea solidifies. This temporal dance between different brain rhythms appears to support the emergence of novel, creative metaphors.

“Generating creative ideas to achieve a goal is a complex process,” Lai and Yu told PsyPost. “It evolves over time and sometimes involves paradoxical processes. To generate more creative metaphors, as we showed in the study, the brain first exhibits more synchronization in a type of neural oscillation known for inhibiting distractions. But later in the process, the oscillation flips the sign (i.e., more resynchronization), suggesting neural excitation immediately before reporting a creative metaphor.”

The study also highlights the benefits of using dynamic modeling approaches to capture the flow of brain activity over time. Traditional EEG analyses often average signals across trials or time windows, which can obscure the sequence of mental events during sustained thought. By using a hidden Markov model, the researchers were able to untangle these overlapping processes and better understand how the brain orchestrates complex cognitive tasks like metaphor generation.

“It is exciting to see the different involvement of the same neural process, known as the alpha-band oscillation, depending on what stage of generation a person is in,” the researchers said. “This finding consolidates previous theories. It is well known that the neural synchronization in alpha-band is critical for creativity. It has also been shown that the desynchronization in the same band marks excitation. We managed to consolidate the multifaceted roles of the same type of oscillation by focusing on the temporal dynamics in electrophysiological data that comes with high temporal resolution.”

Despite its strengths, the study has some limitations. While the results support a role for alpha oscillations in creativity, the findings related to gamma-band activity are more tentative and need to be replicated in future work. The crowd ratings of metaphor novelty also had lower reliability than ratings of aptness, which could have reduced sensitivity to detect some effects. Additionally, while the study focused on metaphor generation, it remains unclear whether similar brain dynamics would be observed for other types of creative comparison, such as literal analogies.

"We have conducted quantitative analysis of the brain data so far," Lai and Yu explained. "The next step is to conduct qualitative analysis of the linguistic data, namely, the metaphors created by the study participants. By associating types of metaphors with patterns of brain oscillation, we hope to uncover finer grained details of verbal creativity in the brain."

The study, "Hidden Brain States Reveal the Temporal Dynamics of Neural Oscillations During Metaphor Generation and Their Role in Verbal Creativity," was authored by Yuhua Yu, Lindsay Krebs, Mark Beeman, and Vicky T. Lai.

Scientists map the hidden architecture of the brain's default mode network

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A new study published in *Nature Neuroscience* sheds light on the structural foundations of the brain's default mode network, a system of regions long associated with internally focused thought, memory, and self-reflection. Using postmortem brain tissue and advanced neuroimaging, researchers found that this network is composed of distinct anatomical types of brain tissue, each with different roles in processing information. The findings help explain why the default mode network is involved in such a wide variety of mental states—from introspection to decision-making—and suggest that its structure enables a unique balance of communication across the brain.

The default mode network, or DMN, is one of the most widely studied yet poorly understood brain systems in neuroscience. It was originally discovered through brain scans showing that certain regions become less active when a person focuses on an external task, like solving a math problem. But over time, researchers noticed these same regions were also active during a wide range of cognitive activities, such as daydreaming, remembering the past, imagining the future, and even making complex decisions. This unexpected versatility raised fundamental questions about what the DMN does and how it manages to participate in such seemingly contradictory mental functions.

One key to solving this puzzle, the researchers hypothesized, lies in the network's anatomy. Much of the past research on the DMN has used functional MRI to track patterns of activity, but less attention has been paid to the underlying microstructure that might shape those functions. The authors of the new study believed that a deeper understanding of the DMN's cellular and anatomical features could clarify how it supports such a diverse array of mental processes.

"The default mode network has a fascinating history in neuroscience. It was first identified as a group of brain regions that become less active when people engage in a specific task," explained study author Casey Paquola, the head of the Multiscale Neurodevelopment Lab at the Institute of Neuroscience and Medicine (INM-7) at the Helmholtz Associations' Research Center Jülich.

"But over time, researchers noticed that these same regions were actually activated during a wide variety of tasks — from recognizing faces to making decisions. This led to a lot of diverse theories about what the DMN is and what its role is in cognition. So, despite being discussed in tens of thousands of studies since 2001, it remained enigmatic."

“Notably, the vast majority of those studies used fMRI to study the DMN. As I work at the intersection of neuroanatomy and neuroimaging, I thought it would be a novel angle to investigate this functional entity through the lens of neuroanatomy. We wanted to test whether the hypotheses based on functional MRI were supported or rejected based on the architecture of the DMN.”

To do this, the research team combined two powerful tools: postmortem brain histology and in vivo neuroimaging. The histological data came from a high-resolution 3D reconstruction of a human brain donated after death, allowing for precise mapping of cell densities and tissue types across the cortex. The team analyzed nearly 7,400 thinly sliced brain sections, stained to reveal the shapes and layers of cells, and reconstructed them into a 3D model known as “BigBrain.” These anatomical maps were then compared with functional brain networks defined by resting-state MRI scans in living participants.

The researchers focused on how different parts of the DMN varied in their cytoarchitecture—the arrangement and characteristics of cells across different layers of the cortex. They identified several types of cortical microstructure within the DMN, ranging from areas specialized for processing sensory information to regions associated with memory and internal thought. This showed that the DMN is not uniform but rather includes a mix of cell types, each potentially suited for different tasks.

Using data-driven modeling, the team found a spectrum—or axis—of cytoarchitectural variation across the DMN. Some regions had highly layered structures with dense mid-level cell populations, while others had flatter, less differentiated profiles. These differences aligned with known anatomical types, such as eulaminate regions that process external information and agranular areas often linked to self-generated thought and emotion.

The researchers then examined how these anatomical differences relate to the DMN’s connectivity. By analyzing diffusion MRI data from healthy adults, they assessed how efficiently information could travel along structural pathways linking different brain regions. They found that parts of the DMN with highly layered cytoarchitecture were more strongly connected to other brain regions, particularly those involved in sensory processing. These regions appeared to serve as “receivers,” efficiently gathering input from across the brain.

In contrast, areas with flatter cytoarchitecture were relatively isolated from sensory input, suggesting that they form an “insulated core” within the DMN. These more internally focused regions, like the anterior cingulate cortex, may support self-referential processing or maintain mental representations that are less dependent on immediate sensory information.

To further understand the flow of information within the DMN, the researchers used a modeling technique called regression dynamic causal modeling. This method estimates how activity in one brain region influences another, providing a measure of functional input and output. The results confirmed that “receiver” regions in the DMN received strong input from a variety of other brain systems, while the more insulated areas were relatively unaffected by outside signals.

Perhaps most strikingly, the researchers found that the DMN differs from other brain networks in how it sends information back out. While many networks tend to favor certain types of connections, the DMN distributed its output evenly across all levels of the brain’s processing hierarchy—from low-level sensory areas to high-level association regions. This suggests that the DMN plays a unique integrative role, capable of influencing thought and behavior at multiple levels.

To verify that these patterns weren’t just artifacts of group-level analyses, the team conducted a replication study using ultra-high field 7-Tesla MRI in individual participants. This allowed them to map microstructural variation and connectivity within each person’s brain. The results were consistent with the earlier findings, supporting the idea that the DMN’s unique structure and connectivity patterns are present at the level of individual brains.

“Given the DMN is largely expanded in humans relative to other mammals, more so than any other functional network, an interesting take-away from this study is that this unique network of brain regions is capable of enriching our interpretation of the world, by coloring our world view with other types of information, from autobiographical memory or social perspectives,” Paquola told PsyPost. “In other words, this network operates in a very different way to standard sensory processing, and that may help humans to have a richer understanding of the world around us.”

But as with all research, there are limitations. The detailed anatomical mapping was based on a single postmortem brain, and while replication was attempted with high-resolution imaging in living subjects, further validation across more

diverse samples is needed. The study also focused on healthy adults, leaving open questions about how the DMN might develop during childhood or change in mental illness.

Future research will aim to understand how the DMN's anatomy evolves over time and how it interacts with cognitive development and psychiatric symptoms. For example, if certain subregions mature more slowly or become disrupted in disorders such as depression or schizophrenia, this could help explain why these conditions involve changes in self-perception or thought patterns.

"I'm very interested in how the brain develops, that is how it changes from infancy to adulthood," Paquola said. "Moving forward, we'd like to understand more about how the maturation of the DMN coincides with cognitive maturation and changes in mental health."

The study, "The architecture of the human default mode network explored through cytoarchitecture, wiring and signal flow," was authored by Casey Paquola, Margaret Garber, Stefan Frässle, Jessica Royer, Yigu Zhou, Shahin Tavakol, Raul Rodriguez-Cruces, Donna Gift Cabalo, Sofie Valk, Simon B. Eickhoff, Daniel S. Margulies, Alan Evans, Katrin Amunts, Elizabeth Jefferies, Jonathan Smallwood, and Boris

Neuroscientists discover biological mechanism that helps the brain ignore irrelevant information

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New research published in *Nature Neuroscience* sheds light on how the brain filters out distractions during memory formation. The study reveals that a type of synaptic plasticity—long-term changes in inhibitory connections between neurons—helps the brain suppress irrelevant sensory input during memory replay, a process believed to support long-term learning. This filtering mechanism allows the hippocampus to focus on the general structure of past experiences, rather than the noisy or unpredictable details.

The researchers wanted to understand how the brain distinguishes between useful and irrelevant information when storing memories. While it is well established that the hippocampus replays neural activity to consolidate memories, what actually gets replayed—and how the brain decides what to keep

or discard—remains unclear. This study aimed to uncover the neural rules that shape the content of these replay events, particularly how distractions are suppressed while core patterns are preserved.

To investigate this, the research team used a combination of computational models and experimental methods in mice. First, they built three types of models—a basic spiking network, a detailed biophysical model of hippocampal neurons, and an abstract mathematical model. Each model simulated memory replay in the hippocampus, focusing on an area called CA3, which is known for generating sharp-wave ripples—brief bursts of brain activity linked to memory consolidation. These models were trained on sequences of experiences containing both relevant spatial patterns and irrelevant, randomly placed cues.

In each simulation, the models learned to represent the environment using a Hebbian learning rule. This rule strengthens connections between neurons that activate together, and in this study, it was applied not only to excitatory synapses but also to inhibitory ones—a departure from most previous models.

The team found that including inhibitory plasticity allowed the network to suppress the activity of neurons tuned to unpredictable, non-generalizable stimuli, while still reinforcing patterns that reflected stable aspects of the environment. In contrast, networks without inhibitory plasticity replayed noisy and disorganized sequences that did not resemble meaningful memories.

To test the predictions of their models in real brains, the researchers conducted optogenetic experiments in mice. They implanted tiny optical fibers and injected viruses to target specific neurons in the hippocampus with light-sensitive proteins. By pairing random sensory cues with artificial stimulation of a sparse group of neurons, they effectively created artificial “distractor cells.” These neurons became active during irrelevant stimuli.

Later, during periods of rest when memory replay typically occurs, the researchers measured whether these neurons were suppressed. As predicted, neurons artificially linked to unpredictable stimuli showed reduced activation during memory replay, consistent with the idea that the brain learns to inhibit irrelevant representations.

The experimental data also confirmed that this suppression was linked to increased inhibitory input onto these neurons. Cells that responded to random

cues received stronger inhibitory signals than place cells, which are known to represent consistent features like spatial location. This supports the idea that inhibitory synapses adapt based on experience and help shape the content of memory replay in a way that supports generalization.

In both simulations and biological experiments, when inhibitory plasticity was removed or disrupted, the brain's ability to distinguish signal from noise broke down. Replay became cluttered with irrelevant information, and the networks failed to maintain clean, structured representations. This suggests that inhibitory learning is not only important for filtering distractions but also essential for the formation of coherent memories.

The study also introduced a simplified model that abstracted real-world learning into a sequence of observations with both consistent patterns and random distractions. In this model, excitatory learning alone could not filter out noise. But when inhibition was allowed to adapt based on the timing of neural activity, the network learned to suppress unpredictable inputs over time. The more often a distractor occurred in different contexts, the more inhibition it accumulated, eventually blocking it from being replayed. This mechanism aligns with the idea that memory consolidation prioritizes generalizable information—patterns that remain stable across multiple experiences.

While the study provides strong support for the role of inhibitory plasticity in memory consolidation, it also has limitations. The researchers used relatively simple environments and focused on a specific hippocampal circuit. In real life, experiences are far more complex, and many different brain areas are involved in processing and storing memories.

Additionally, the study treated inhibitory neurons as a uniform group, while in reality, there are many subtypes with different roles. Future research could explore how different types of inhibitory neurons contribute to memory selection and whether this mechanism applies in other brain regions or during sleep.

The study, "Inhibitory plasticity supports replay generalization in the hippocampus," was authored by Zhenrui Liao, Satoshi Terada, Ivan Georgiev Raikov, Darian Hadjiabadi, Miklos Szoboszlay, Ivan Soltes, and Attila Losonczy.

Your left and right brain hear language differently. A neuroscientist explains how

Credit: Pixabay/CC0 Public Domain

Some of the most complex cognitive functions are possible because different sides of your brain control them. Chief among them is speech perception, the ability to interpret language. In people, the speech perception process is typically dominated by the left hemisphere.

Your brain breaks apart fleeting streams of acoustic information into parallel channels—linguistic, emotional and musical—and acts as a biological multicore processor. Although scientists have recognized this division of cognitive labor for over 160 years, the mechanisms underpinning it remain poorly understood.

Researchers know that distinct subgroups of neurons must be tuned to different frequencies and timing of sound. In recent decades, studies on animal models, especially in rodents, have confirmed that splitting sound processing across the brain is not uniquely human, opening the door to more closely dissecting how this occurs.

Yet a central puzzle persists: What makes near-identical regions in opposite hemispheres of the brain process different types of information?

Answering that question promises broader insight into how experience sculpts neural circuits during critical periods of early development, and why that process is disrupted in neurodevelopmental disorders.

Timing is everything

Sensory processing of sounds begins in the cochlea, a part of the inner ear where sound frequencies are converted into electricity and forwarded to the auditory cortex of the brain. Researchers believe that the division of labor across brain hemispheres required to recognize sound patterns begins in this region.

For more than a decade, my work as a neuroscientist has focused on the auditory cortex. My lab has shown that mice process sound differently in the left and right

hemispheres of their brains, and we have worked to tease apart the underlying circuitry.

For example, we've found the left side of the brain has more focused, specialized connections that may help detect key features of speech, such as distinguishing one word from another. Meanwhile, the right side is more broadly connected, suited for processing melodies and the intonation of speech.

We tackled the question of how these left-right differences in hearing develop in our latest work, and our results underscore the adage that timing is everything.

We tracked how neural circuits in the left and right auditory cortex develop from early life to adulthood. To do this, we recorded electrical signals in mouse brains to observe how the auditory cortex matures and to see how sound experiences shape its structure.

Surprisingly, we found that the right hemisphere consistently outpaced the left in development, showing more rapid growth and refinement. This suggests there are critical windows of development—brief periods when the brain is especially adaptive and sensitive to environmental sound—specific to each hemisphere that occur at different times.

To test the consequences of this asynchrony, we exposed young mice to specific tones during these sensitive periods. In adulthood, we found that where sound is processed in their brains was permanently skewed. Animals that heard tones during the right hemisphere's earlier critical window had an overrepresentation of those frequencies mapped in the right auditory cortex.

Adding yet another layer of complexity, we found that these critical windows vary by sex. The right hemisphere critical window opens earlier in female mice, and the left hemisphere window opens just days later. In contrast, male mice had a very sensitive right hemisphere critical window, but no detectable window on the left. This points to the elusive role sex may play in brain plasticity.

Our findings provide a new way to understand how different hemispheres of the brain process sound and why this might vary for different people. They also provide evidence that parallel areas of the brain are not interchangeable: the brain can encode the same sound in radically different ways, depending on when it occurs and which hemisphere is primed to receive it.

Speech and neurodevelopment

The division of labor between brain hemispheres is a hallmark of many human cognitive functions, especially language. This is often disrupted in neuropsychiatric conditions such as autism and schizophrenia.

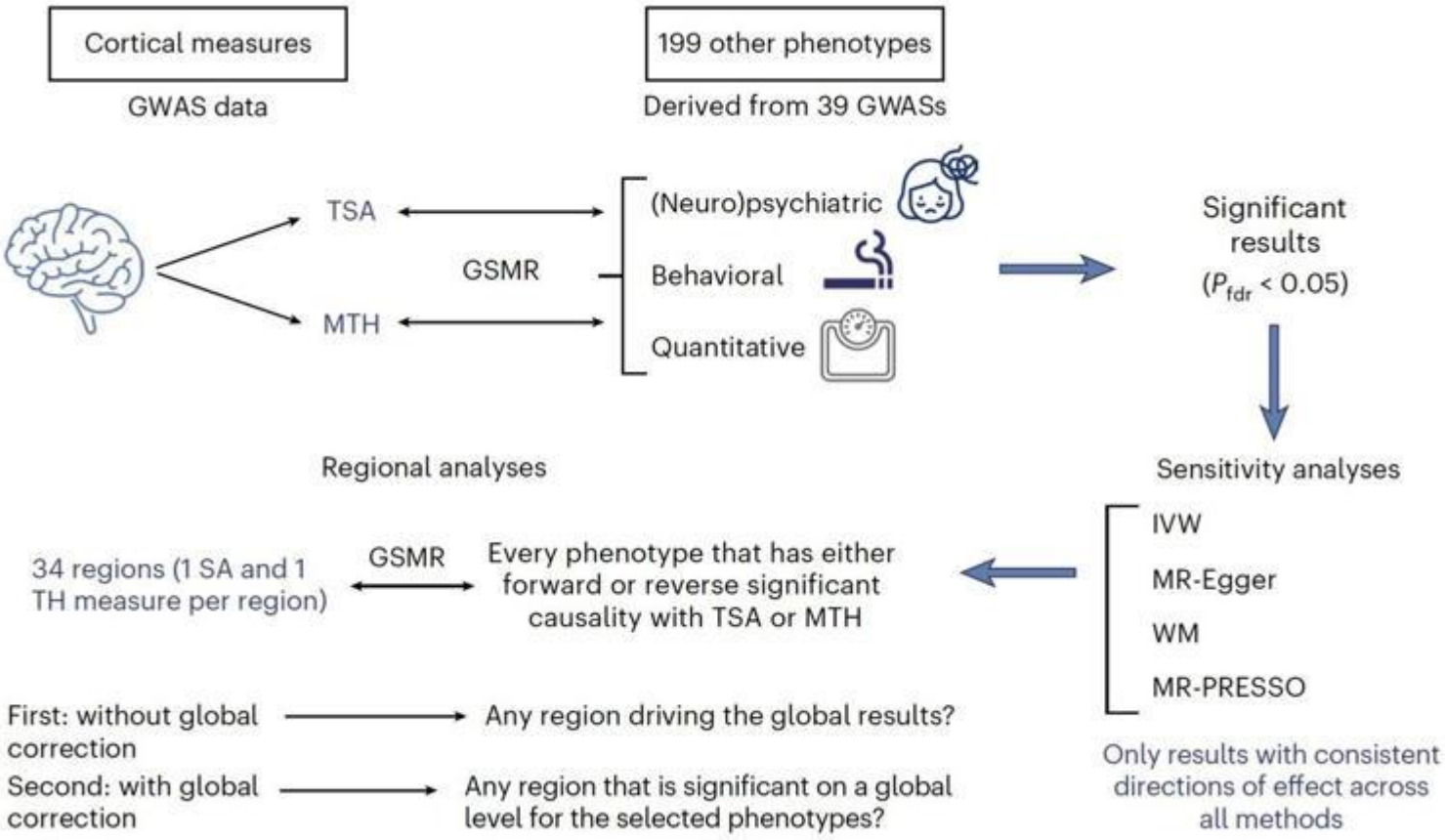
Reduced language information encoding in the left hemisphere is a strong indication of auditory hallucinations in schizophrenia. And a shift from left- to right-hemisphere language processing is characteristic of autism, where language development is often impaired.

Strikingly, the right hemisphere of people with autism seems to respond earlier to sound than the left hemisphere, echoing the accelerated right-side maturation we saw in our study on mice. Our findings suggest that this early dominance of the right hemisphere in encoding sound information might amplify its control of auditory processing, deepening the imbalance between hemispheres.

These insights deepen our understanding of how language-related areas in the brain typically develop and can help scientists design earlier and more targeted treatments to support early speech, especially for children with neurodevelopmental language disorders.

Provided by The Conversation

Brain cortex structure linked to mental abilities and psychiatric disorders



Overview of the design of the team's study. Credit: Lin et al. (Nature Mental Health, 2025).

The cerebral cortex, the outermost layer of the brain, is the central driver of various human capabilities, including decision-making, perception, language and memory. Understanding how the morphology (i.e., structure and shape) of people's cerebral cortex is related to their mental health is a long-standing goal for many neuroscientists, as it could help to predict the risk that people will develop specific neuropsychiatric conditions while also contributing to their diagnosis and potentially informing their treatment.

Researchers at Maastricht University Medical Centre, Utrecht University and other institutes recently carried out a study aimed at unveiling causal relationships between cortical morphology and traits, including both neuropsychiatric

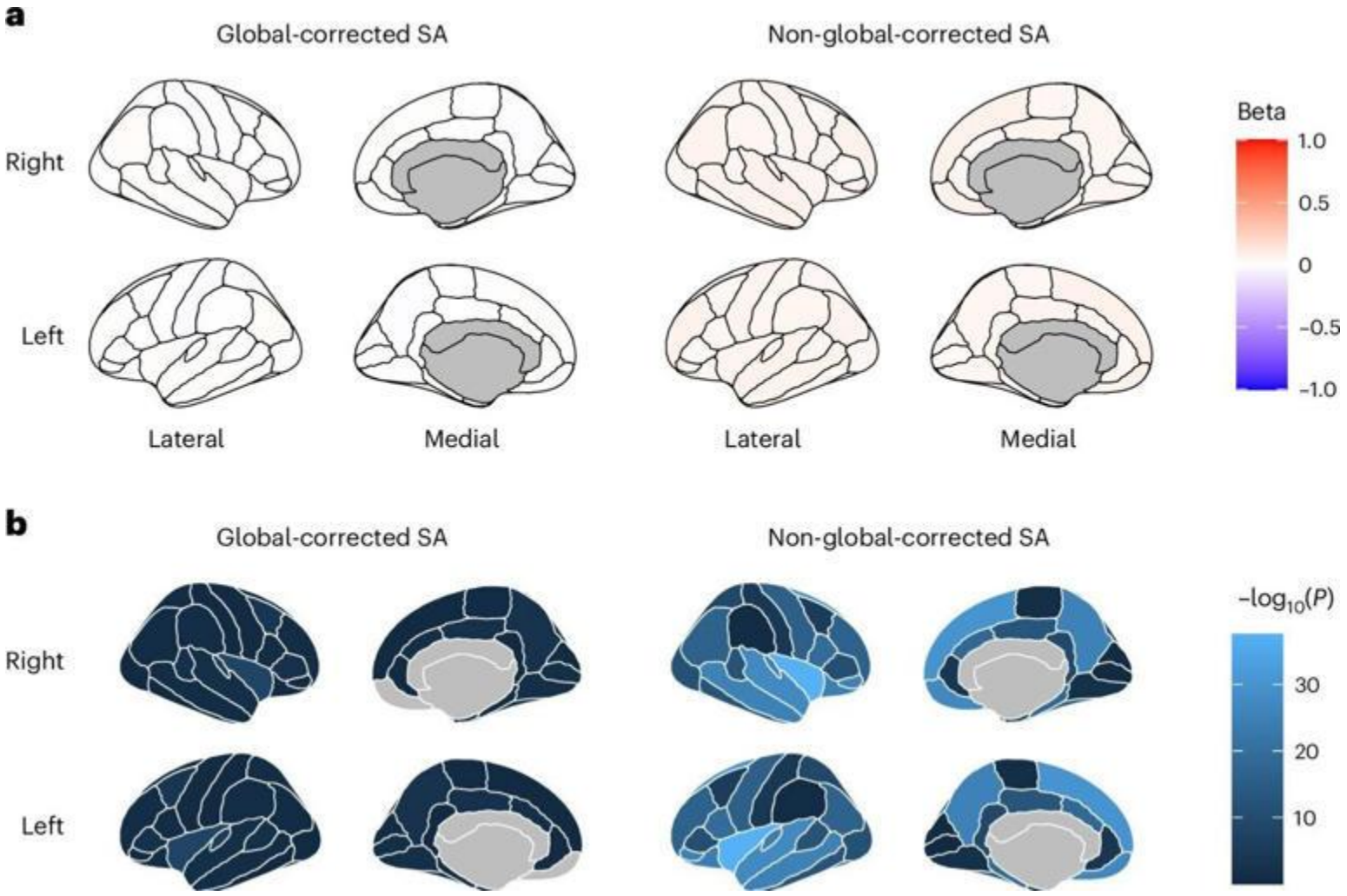
conditions, behavioral patterns and metabolic traits. Their findings, published in *Nature Mental Health*, suggest that the total surface area (TSA) of the cerebral cortex and mean cortical thickness (MCT) contribute to people's mental abilities and the development of some severe mental health disorders, respectively.

"Brain cortical morphology, indexed by its surface area and thickness, is known to be highly heritable," wrote Bochao Danae Lin, Yunzhi Li and their colleagues in their paper. "Previous research has suggested a relationship of cortical morphology with several neuropsychiatric phenotypes. However, the multitude of potential confounders makes it difficult to establish causal relationships."

As part of their study, the researchers analyzed a large amount of data sourced from a large genome-wide database, which was compiled as part of the Enhancing Neuro-Imaging Genetics through Meta-Analysis (ENIGMA) study. This is a brain-imaging study that collected brain imaging data, as well as psychiatric, psychological, behavioral and metabolic information from individuals living in 43 countries worldwide.

"We employ generalized summary-data-based Mendelian randomization and a series of sensitivity analyses to investigate causal links between 70 cortical morphology measures and 199 neuropsychiatric, behavioral and metabolic phenotypes," wrote Lin, Li and their colleagues. "We show that total brain cortical surface area (TSA) has significant positive causal effects on 18 phenotypes."

To analyze the data sourced from the ENIGMA database, Lin, Li and their colleagues employed a statistical technique called Mendelian randomization, which is useful for estimating causal relationships between traits while also controlling for potentially confounding factors. Their findings suggest that the TSA of the cerebral cortex is in fact causally related to some mental abilities, particularly their cognitive performance (i.e., how well they can memorize information, their ability to focus on specific tasks, their reasoning skills and other mental capabilities).



Regional plots for SA with CP. Credit: Nature Mental Health (2025). DOI: 10.1038/s44220-025-00397-4

"The strongest effects include TSA positively influencing cognitive performance, while reverse analyses reveal small effects of cognitive performance on TSA," wrote Lin, Li and their colleagues.

"Global mean cortical thickness (MTH) exhibits significant causal effects on five phenotypes, including schizophrenia. MTH reduces schizophrenia risk, and bidirectional causality is found between MTH and smoking initiation. Finally, in regional analyses, we detect positive influences of the transverse temporal surface area on cognitive performance and negative influences of transverse temporal thickness on schizophrenia risk."

Overall, the results of the analyses performed by this team of researchers suggest that cortical morphology does in fact affect both people's mental capabilities and neuropsychiatric traits. The causal relationships identified by Lin, Li and his

colleagues could be explored further in future neuroscience studies, potentially helping to improve the early diagnosis and treatment of specific disorders, including schizophrenia and some cognitive deficits.

"Our results highlight bidirectional associations between TSA, MTH and neuropsychiatric traits," wrote Lin, Li and their colleagues. "These insights offer potential avenues for intervention studies aimed at improving brain health."

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More information: Bochao Danae Lin et al, Dissecting causal relationships between cortical morphology and neuropsychiatric disorders: a bidirectional Mendelian randomization study, *Nature Mental Health* (2025). DOI: 10.1038/s44220-025-00397-4.

Neuroscientists remain steadfastly uncertain about how the brain encodes memory

Researchers from Monash University, in collaboration with the European Biostasis Foundation and Apex Neuroscience, have revealed that although most neuroscientists agree that long-term memories depend primarily on neuronal connectivity patterns, significant uncertainties persist regarding precisely how these memories are structurally encoded.

Brains can retain memories for days, months and even across a lifetime of decades, through mechanisms that remain elusive to those at the cutting edge of neuroscience. Long-term memory enables animals to shape behaviors by linking past experiences with present contexts.

There are fragile memories, like recalling the name of someone you just met, or the location of where the keys were set down, that can seemingly escape the brain's data capture. And there are durable memories that can survive periods of global neuronal inactivity and disruption, indicating that ongoing neural activity is not required to maintain stored information.

Distinctions between memory formation and recall also suggest that stable structural changes, rather than transient biochemical processes, underpin long-term retention.

Over the last century, numerous candidates have been proposed as the physical basis of memory storage. Structural alterations span a broad spectrum, from modifications of individual proteins and ion channels to large-scale changes in synaptic connectivity.

Proposed mechanisms include synaptic strength adjustments, synaptogenesis, intracellular molecular modifications, changes in neuronal excitability, and alterations to myelination or extracellular matrix components.

Some researchers assert that ensembles of synaptic connections form a definitive memory trace. Evidence from perturbations such as hypothermia, where fine

neural structures transiently disappear without memory loss, raises doubts about the exclusivity of synaptic ensembles as memory substrates.

Many of the proposed mechanisms may coexist, collaborate or compensate for one another, complicating efforts to isolate a singular physical structure for how memory is stored.

After 100 years of study, neuroscientists lack consensus on which neurophysiological features encode long-term memories: whether a structural scale exists between molecular details and macroscopic brain features, and whether memory depends on precise molecular states or coarser patterns of connectivity, leaving the field in a persistent state of uncertainty.

Even in a field of competing hypotheses and conflicting certainties, there must be some level of consensus. So, what exactly are the consensus points in theoretical neuroscience?

In the study, "What are memories made of? A survey of neuroscientists on the structural basis of long-term memory," published in *PLOS One*, researchers designed a survey to gauge expert consensus regarding memory's physical underpinnings with questions about memory preservation and extraction.

Researchers recruited 312 neuroscientists from two distinct groups. One cohort comprised 33 "Engram Experts" who had published research directly related to memory neurophysiology. A second group included 279 attendees of the Computational and Systems Neuroscience (COSYNE) conferences from 2022 to 2024, representing a broader range of neuroscience specializations.

Email invitations reached 305 Engram Experts, yielding 33 responses and a 12.1% response rate. Contact was made with 4,125 COSYNE attendees, resulting in 279 responses and a 7.3% response rate. Completion rates for both cohorts hovered near 75%. Monetary incentives of $75 for Engram Experts and $20 for COSYNE participants aimed to improve response rates.

Participants answered 28 questions organized into six sections: demographics; beliefs about the structural basis of memory; theoretical implications of memory storage; brain preservation; whole brain emulation feasibility; and familiarity with relevant topics. Most questions required responses, with optional fields allowing additional commentary.

To address fundamental yet provocative concepts in neuroscience, there were survey questions asked around the concept of structure. Could detailed maps of neuronal structure alone contain specific memories—such as a learned route through a maze or a memorized password? Around 46% of respondents agreed this was theoretically possible, provided sufficiently sophisticated methods existed. Roughly a third strongly disagreed.

Respondents identified additional information potentially necessary for memory readout, most frequently citing dynamically changing neuronal activity patterns (47%), contextual data on experiences and mental states (43%), and sensory-motor information (37%). Less frequently selected were chemical and electrical gradients (15%) and quantum-level properties (5%).

A majority of 70% agreed that lasting changes in neuronal connectivity and synaptic strength primarily constitute the structural basis of long-term memories, as opposed to molecular or subcellular details.

When asked which physical details would have to be measured in order to decode a specific long-term memory from a static, preserved brain, agreement rose with scale and resolution.

A majority of respondents judged that the types and precise locations of individual biomolecules must be captured. Nearly everyone agreed that sub-cellular structures of ~500 nm and larger are indispensable, while atomic or quantum-level particulars were generally viewed as unnecessary for decoding memory.

Turning to practical implications, the survey probed whether current brain preservation methods might someday permit memory decoding.

The survey found a median 41% belief (as a probability) that brains preserved using aldehyde-stabilized cryopreservation (ASC) retain sufficient information to decode some long-term memories. Responses exhibited a bimodal distribution with peaks near 10% and 75%, suggesting respondents held dramatically split views.

Participants estimated a 40% median probability that a whole brain emulation could (eventually) be created from an ASC-preserved brain without prior

electrophysiological recordings, increasing to 62% if such recordings were available beforehand.

Interestingly, neither research background, experimental versus computational, nor expertise level significantly influenced respondents' perspectives. Expert memory researchers were somewhat more skeptical of decoding memories from preserved brains, but the difference was not statistically significant.

Participants were asked to predict when whole brain emulations might become achievable, estimating median timelines for various species. Predictions converging on whole brain emulations of the worm Caenorhabditis elegans suggest it would likely be achieved by 2045, mice by 2065, and humans by 2125.

Most neuroscientists endorse the notion that long-term memories reside in stable structural features of the brain, primarily involving lasting changes in neuronal connectivity and synaptic strength. Yet, substantial disagreement persists about which specific neurophysiological features or at which spatial scale critical physical substrates of long-term memory storage are contained.

Estimates for the theoretical feasibility of decoding memories from preserved brains or creating whole brain emulations varied widely, indicating unresolved fundamental questions.

According to the researchers, the absence of consensus within neuroscience is not itself a problem, but the result of research setting off in different directions in attempts to fill the profound gaps in neuroscientific knowledge about memory's physical basis.

They suggest that advances in observational technologies and computational neuroscience may ultimately clarify these disparate ambiguities.

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More information: Ariel Zeleznikow-Johnston et al, What are memories made of? A survey of neuroscientists on the structural basis of long-term memory, *PLOS One* (2025). DOI: 10.1371/journal.pone.0326920

Scientists discover quantum computing in the brain

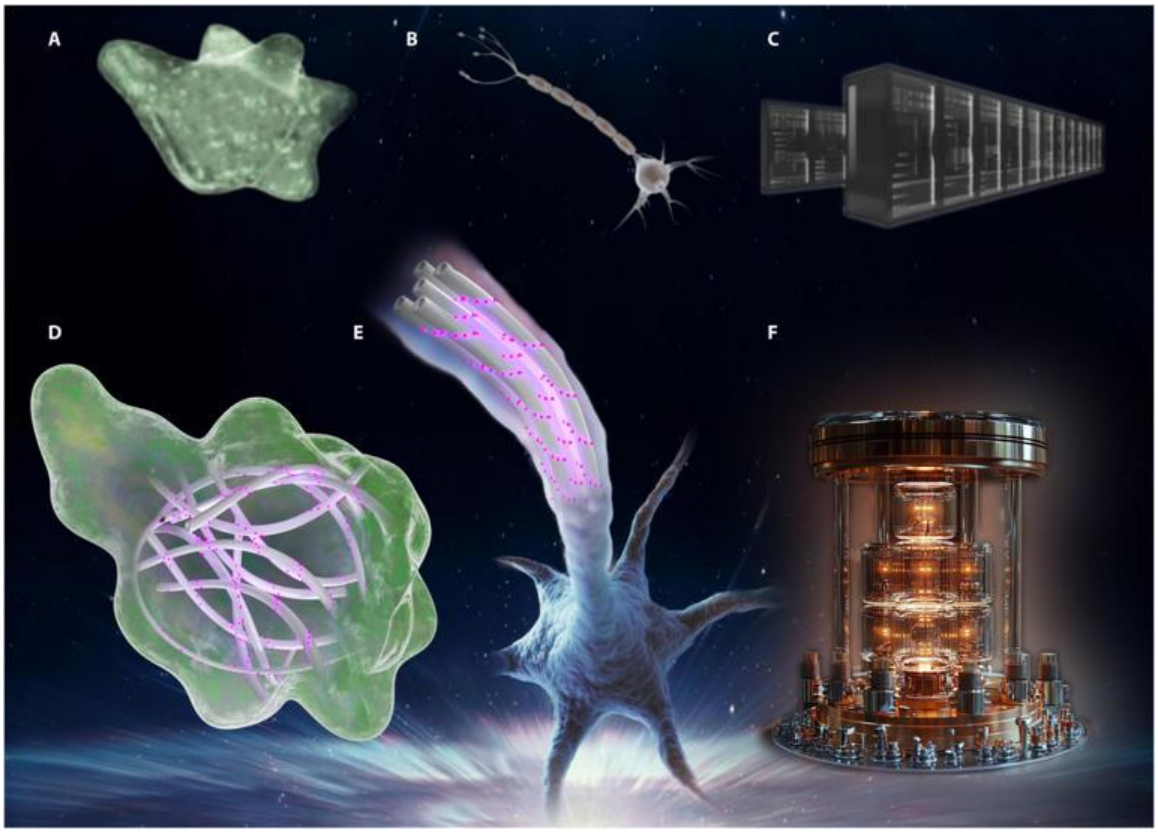
Tryptophan-rich structures in your cells may be doing more than protecting you—they might be computing at quantum speeds. (CREDIT: Gerd Altmann from Pixabay)© The Brighter Side of News

When a molecule of tryptophan absorbs ultraviolet light, it glows faintly as it releases energy at a lower frequency. This effect, called fluorescence, is well known. But something extraordinary happens when many tryptophan molecules act together in highly ordered protein structures: they begin to glow brighter and faster than they should. This surprising group behavior, called superradiance, is the focus of new research that could change how we think about life and the nature of information itself.

Researchers have now found that tryptophan-rich proteins, especially in brain cells and other biological systems, may function as quantum computing networks. These networks not only help protect cells from damage but might also store and transmit data in ways faster and more efficient than previously believed.

The Quantum Surprise in a Noisy World

Quantum effects are usually thought to exist only in small, cold, and controlled systems. Quantum computers, for example, must operate at temperatures colder than outer space to prevent interference. Heat and chaos typically destroy the delicate properties needed for quantum behavior.



Living systems maintain information-processing architectures using photoexcited quantum degrees of freedom. (CREDIT: Science Advances)© The Brighter Side of News

Living systems, on the other hand, are anything but quiet. They are warm, active, and full of chemical noise. Cells, proteins, and neurons are far too large by quantum standards. Yet, a team led by Philip Kurian, founding director of the Quantum Biology Laboratory at Howard University, has found strong evidence that life not only tolerates quantum effects—it may depend on them.

Kurian's team has shown that giant networks of tryptophan molecules, arranged in microtubules, centrioles, and neuron bundles, can behave as quantum optical systems.

Their findings, published in Science Advances, suggest that superradiance—previously only confirmed in atomic systems—can also appear in warm, living matter.

"This work connects the dots among the great pillars of twentieth century physics—thermodynamics, relativity, and quantum mechanics—for a major paradigm shift," said Kurian.

Why Tryptophan Is Special

Tryptophan is not just another amino acid. It has a unique indole ring structure, making it especially good at absorbing ultraviolet light. It also fluoresces with a strong Stokes shift, meaning the light it emits is clearly separated in color from the light it absorbs. These properties make it a favorite tool in laboratory studies of protein behavior.

But tryptophan isn't just helpful in a test tube. It appears naturally in key locations in living systems—often at the interface between water and lipids in cell membranes. It's found in transmembrane proteins, photoreceptors, hemoglobin, and especially in the complex cytoskeletal structures inside cells. These include microtubules and centrioles, which help cells divide, change shape, and move.

Kurian's group studied these mesoscale networks—structures containing over 100,000 tryptophan molecules—and found that they often display a collective optical response. The more ordered the structure, the stronger the quantum effect. And even when they introduced disorder, the effects still survived under normal biological temperatures.

A cell seen under microscope. (CREDIT: Fayette Reynolds M.S. / Pexels)© The Brighter Side of News

Professor Majed Chergui of École Polytechnique Fédérale de Lausanne, who led the experimental team, explained: "It took very precise and careful application of

standard protein spectroscopy methods, but guided by the theoretical predictions of our collaborators, we were able to confirm a stunning signature of superradiance in a micron-scale biological system."

How Living Systems May Use Quantum Light

Kurian's group believes these large tryptophan networks may have evolved to take advantage of their quantum properties. When cells breathe using oxygen—a process called aerobic respiration—they create free radicals, or reactive oxygen species (ROS). These unstable particles can emit high-energy UV photons, which damage DNA and other important molecules.

Tryptophan networks act as natural shields. They absorb this harmful light and re-emit it at lower energies, reducing damage. But thanks to superradiance, they may also perform this protective function much more quickly and efficiently than single molecules could.

This speed could matter even more in the brain. Traditional neuroscience models say that information is passed between neurons using chemical signals, which take milliseconds to complete. But Kurian's study found that the superradiant signal transfer happens in picoseconds—about a billion times faster.

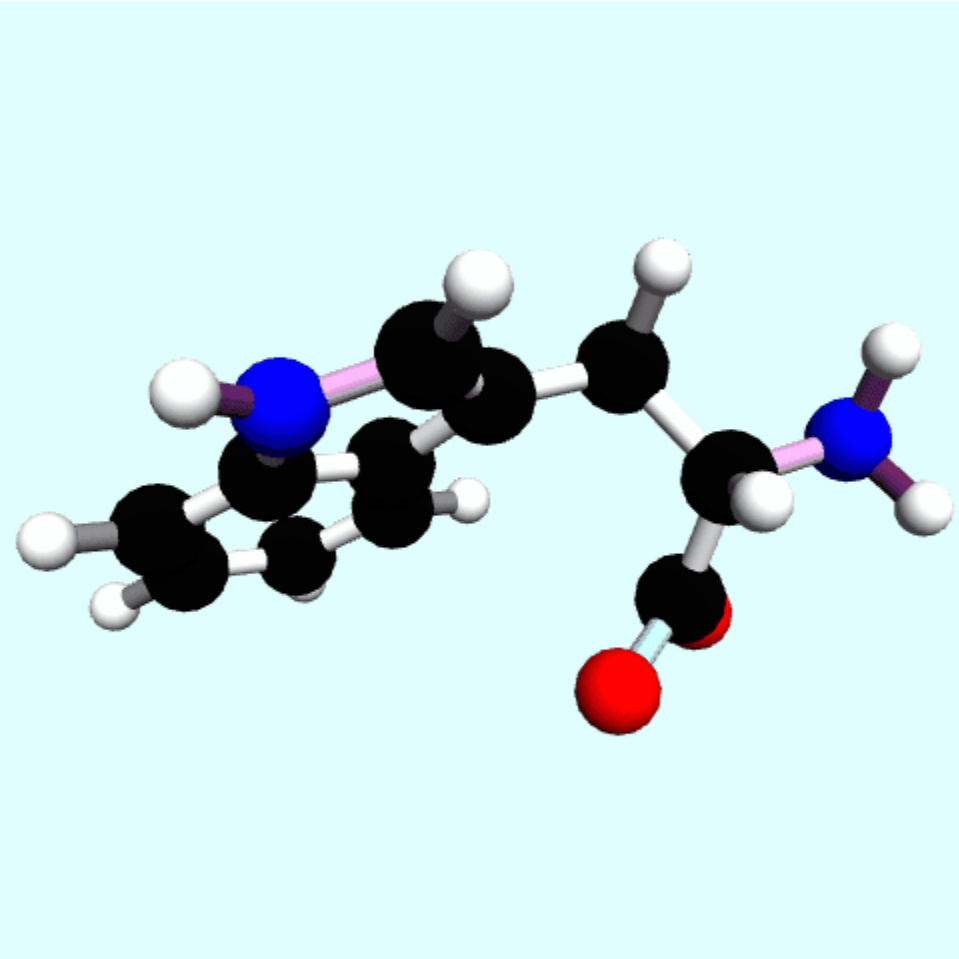
In a previous study, published in The Journal of Physical Chemistry and reported on within The Brighter Side of News, Kurian's team found that these signals might allow cells to share information at speeds and scales that traditional models can't explain. They could act like fiber optic cables, transmitting light-based data through tissues and enabling a new level of biological computing.

"This photoprotection may prove crucial in slowing or stopping degenerative illnesses," said Kurian. "We hope this will inspire a range of new experiments to understand how quantum-enhanced photoprotection plays a role in complex pathologies that thrive on highly oxidative conditions."

A New Kind of Computing

In his paper, Kurian took a bold step: he calculated how much information life on Earth may have processed since its beginning, based on the laws of quantum

mechanics, the speed of light, and the density of matter in the universe. He found that life's information processing—powered by quantum-enhanced structures like tryptophan networks—might rival that of all known matter in the observable cosmos.



Tryptophan ball and stick model spinning. (CREDIT: CC BY-SA 4.0)© The Brighter Side of News

This finding echoes questions raised decades ago by physicist Erwin Schrödinger, who asked in his 1944 book *What is Life?* whether something deeper than chemistry might govern living systems. Kurian's work now offers a possible answer.

Professor Seth Lloyd of MIT, a pioneer in quantum computing, praised the study. "It's good to be reminded that the computation performed by living systems is vastly more powerful than that performed by artificial ones," he said.

Kurian's theories have attracted attention from quantum computing researchers around the world, including Professor Nicolò Defenu of ETH Zurich. "It's really

intriguing to see a vital and growing connection between quantum technology and living systems," Defenu said.

Even space scientists are taking notice. Dante Lauretta, director of the Arizona Astrobiology Center, said that Kurian's predictions offer new insights into the search for life elsewhere in the universe. "The remarkable properties of this signaling and information-processing modality could be a game-changer in the study of habitable exoplanets," he said.

Information-processing modality could be a game-changer in the study of habitable exoplanets. (CREDIT: PHL@UPR Arecibo)© The Brighter Side of News

Going Beyond the Brain

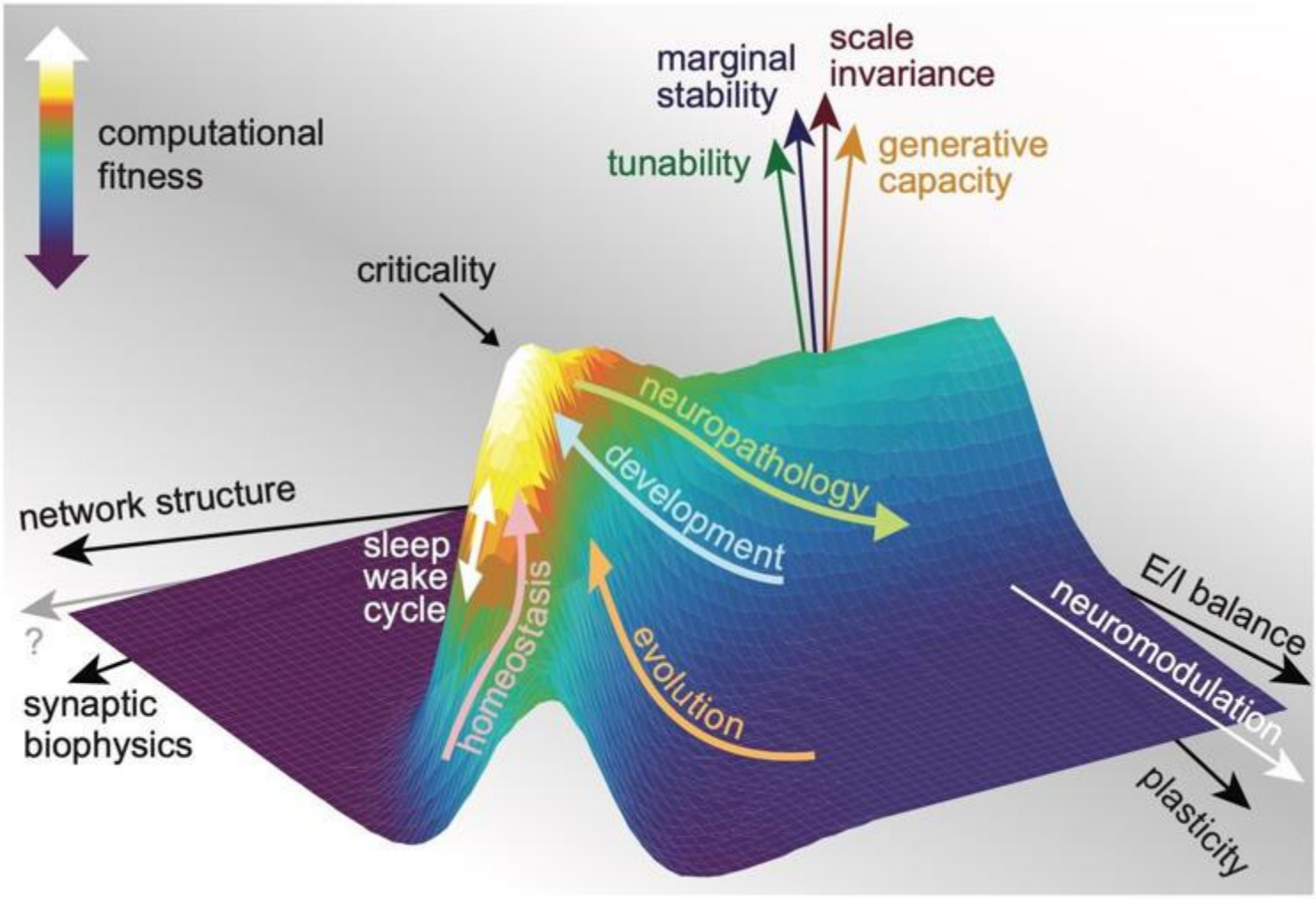
While most studies focus on neurons, Kurian and others remind us that most life on Earth is aneural. Bacteria, plants, fungi, and single-celled organisms form the bulk of the planet's biomass. These living systems may use tryptophan networks and quantum effects just as efficiently as brains do.

The presence of super radiant behavior in these simple organisms suggests that quantum information processing might be a core feature of life itself—not just an add-on for complex beings.

"There are signatures in the interstellar media and on interplanetary asteroids of similar quantum emitters," Lauretta said. "These may be precursors to eukaryotic life's computational advantage."

Kurian hopes this work will spark further research into the quantum dimensions of life. "In the era of artificial intelligences and quantum computers, it is important to remember that physical laws restrict all their behaviors," he said. "And yet, though these stringent physical limits also apply to life's ability to know and simulate the universe, we can still explore and make sense of it. It's awe-inspiring that we get to play such a role."

A unified theory of the mind could be key to understanding brain function and neurological disease



According to Keith Hengen and Woodrow Shew, criticality—a state shaped by evolution, growth, and restorative sleep—marks the peak of the brain's computational power. Credit: Neuron (2025). DOI: 10.1016/j.neuron.2025.05.020

In a new paper with implications for preventing Alzheimer's disease and other neurological disorders, Keith Hengen, an associate professor of biology in Arts & Sciences at Washington University in St. Louis, suggests a new comprehensive

approach to understanding how the brain works and the rules it must follow to reach optimal performance.

"There's a common perception that the human brain is the most complicated thing in the universe," Hengen said. "The brain is immensely powerful, but that power may arise from a relatively simple set of mathematical principles."

Hengen starts with the premise that almost everything our brains do is learned or powerfully shaped by experience. In other words, we aren't born with hard-wired circuits preprogrammed to help us read, drive cars or do anything else that we do every day. A healthy brain must be ready to learn anything and everything.

But how is a collection of neurons capable of learning? Hengen suggests that brains become learning machines only when they reach a special state called "criticality." A concept borrowed from physics, criticality describes a complex system that is at the tipping point between order and chaos. At this razor's edge, brains are primed to gain new information, Hengen said. "Brains need to reach criticality to think, remember and learn."

Hengen proposed criticality as a unifying theory of brain function and disease in the journal *Neuron*. Woodrow Shew, a physicist at the University of Arkansas, is the co-author.

A biologist and a physicist may seem like an odd pairing, but the new unifying theory blends both realms of science. Physicists often describe criticality using the classic example of a sand pile: As sand is added, the pile will grow steeper and steeper until it eventually avalanches. Right before that final grain triggered a moment of chaos, the pile was at a critical angle, one step away from instability.

Shew explained that physicists first developed a deep understanding of criticality as a way to describe magnets and other materials. Around the turn of the 21st century, these ideas were expanded to explain a broader range of complex systems, including avalanches, earthquakes and, ultimately, living systems and the brain.

A defining aspect of critical systems is that they look the same at any scale: A sand pile on the brink of an avalanche has the same slope whether the pile is tiny or mountainous. In the brain, criticality is constant whether it's measured in a handful of neurons or an entire region. Likewise, brain patterns that unfold in

time are startlingly similar when considered in milliseconds or hours. "This matches our intuitive understanding of how brains work," Hengen said. "Our internal experiences span milliseconds to months. They don't have a scale."

Hengen and Shew suggest that criticality isn't just a theoretical concept; it's a state that can be precisely measured and calculated through fMRI brain imaging technology. "Criticality is the optimal computational state of the brain," Hengen said. "We've developed a mathematical way to measure how close the brain is to criticality, which should help us nail down the fundamental questions about how a human brain works."

A new understanding of disease

The criticality framework offers a new perspective for understanding neurological disease. Rather than focusing on specific damaged brain regions or accumulated proteins, Hengen argues that diseases such as Alzheimer's destroy something more basic: the brain's ability to maintain criticality.

"Alzheimer's and other neurodegenerative diseases don't just damage neurons, they break the brain's general ability to compute by slowly dissolving criticality," Hengen explained. "As a brain moves further and further from criticality, it loses the ability to adapt and process information effectively."

This framework explains a puzzling feature of brain diseases: Patients often appear completely normal until they've lost many neurons. "The brain has remarkable compensatory abilities that can mask functional problems even as criticality begins to erode," Hengen said. "Traditional assessments miss the early stages because they focus on established endpoints that the brain tries to maintain through workarounds."

As criticality gradually deteriorates, the brain works harder to achieve the same cognitive outcomes, Hengen said. "It's like an engine that still runs but requires more fuel and generates more heat. By the time we notice memory problems or other symptoms, criticality has likely been compromised for years."

Hengen's collaboration with David M. Holtzman, MD, the Barbara Burton and Reuben M. Morriss III Distinguished Professor at WashU Medicine, has revealed

that tau protein buildup in Alzheimer's directly disrupts criticality, providing a clear link between the disease's molecular hallmarks and cognitive collapse.

This connection between criticality and Alzheimer's opens exciting diagnostic possibilities. In theory, a simple fMRI could help detect breakdowns in criticality years before symptoms appear. "In combination with cutting-edge blood tests, we could identify people at risk and intervene before irreversible damage occurs," Hengen said.

In another collaboration, Hengen has teamed up with Deanna Barch, the Gregory B. Couch Professor of Psychiatry at WashU Medicine and a professor of psychological and brain sciences in Arts & Sciences, for an observational study to see how criticality at birth determines cognitive development and abilities in childhood.

"From the beginning, some kids are closer to criticality than others, which, based on our theory, suggests they are going to be better learners," Hengen said. "Many outside factors can affect their success in school, but criticality can explain an impressive amount of the variability between children."

The sleep-mind connection

In early 2024, Hengen and co-author Ralf Wessel, a professor of physics in Arts & Sciences at WashU, used the concept of criticality to revisit an age-old question: Why do we need sleep? By tracking brain activity over multiple weeks, they found that sleep restores a state of criticality. "Being awake and active moves us away from criticality, and sleep is like a reset button," Hengen explained.

That insight could help researchers unlock the power of sleep as a therapy for Alzheimer's and other neurological diseases that push the brain away from its optimal state. Previous studies by Holtzman and others have found that people who don't get the sleep they need—perhaps due to shift work or chronic insomnia—are at a much higher risk for Alzheimer's as they age. And there's already some evidence that sleep interventions can help slow the progression of Alzheimer's symptoms.

Hengen believes that targeted, intensive sleep-based therapy could help restore criticality and improve learning and memory in people with brain disease. Studies of mice conducted by Holtzman and James McGregor, a postdoctoral researcher in Hengen's lab, offer a glimpse of the possibilities: Mice specifically bred to have symptoms of Alzheimer's become faster learners after a targeted sleep intervention reinforces criticality.

Critical future

There is much work to be done, but Hengen would eventually like to understand how criticality helps explain complex features of human neurobiology. "We may find that someone who is an amazing artist, for example, might be extremely close to criticality in parts of the brain involved in creative ideation," he said. It's also possible that a close look at criticality could point to undiscovered tendencies or talents that just need an outlet. "Maybe they never tried art, but we can see that the potential is there."

In the meantime, Hengen, Shew, and others are spreading the word about the importance of criticality. Hengen presented a TEDx talk on the subject in 2024 and shared his work at Arts & Sciences' inaugural research pitch competition, where he took second place. He hopes the new *Neuron* paper will inspire conversations among neurologists, doctors, reporters and the general public.

A unified theory of the mind could change the world, but first, it must unify the experts. "Woody (Shew) and I really think we're on to something here," Hengen said. "And, perhaps slowly, others are starting to agree."

WashU was the ideal place for a new concept of the brain to emerge, Hengen said. "We're surrounded by brilliant people in diverse fields, including physics, biology, psychology, mathematics and neuroscience, and the community here is remarkably supportive," he said. "Everyone is ready to help."

More information: Keith B. Hengen et al, Is criticality a unified setpoint of brain function?, *Neuron* (2025). DOI: 10.1016/j.neuron.2025.05.020

Provided by Washington University in St. Louis

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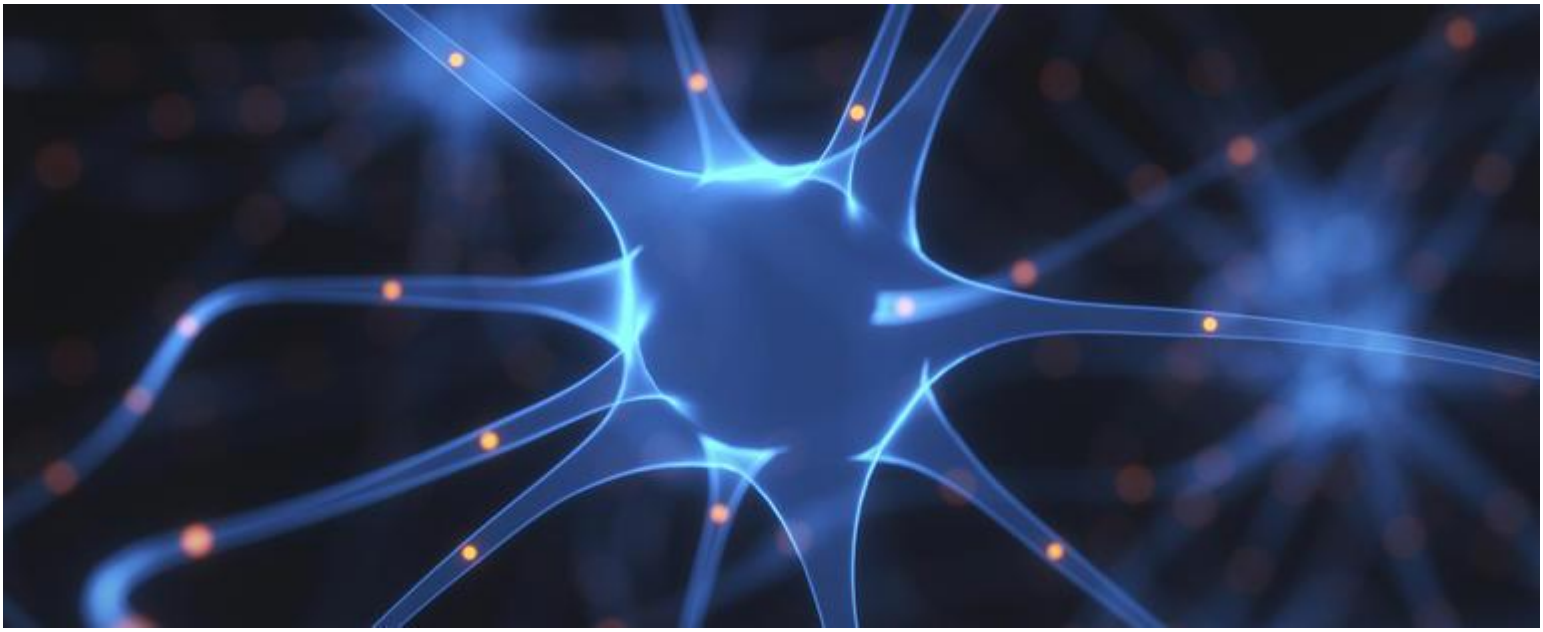
Brain's Memory Center Never Stops Making Neurons, Study Confirms



Brain neuron illustration

Though it's now clear humans continue to grow new brain cells throughout their entire lives, debate persists over whether this applies to specific areas involved with memory.

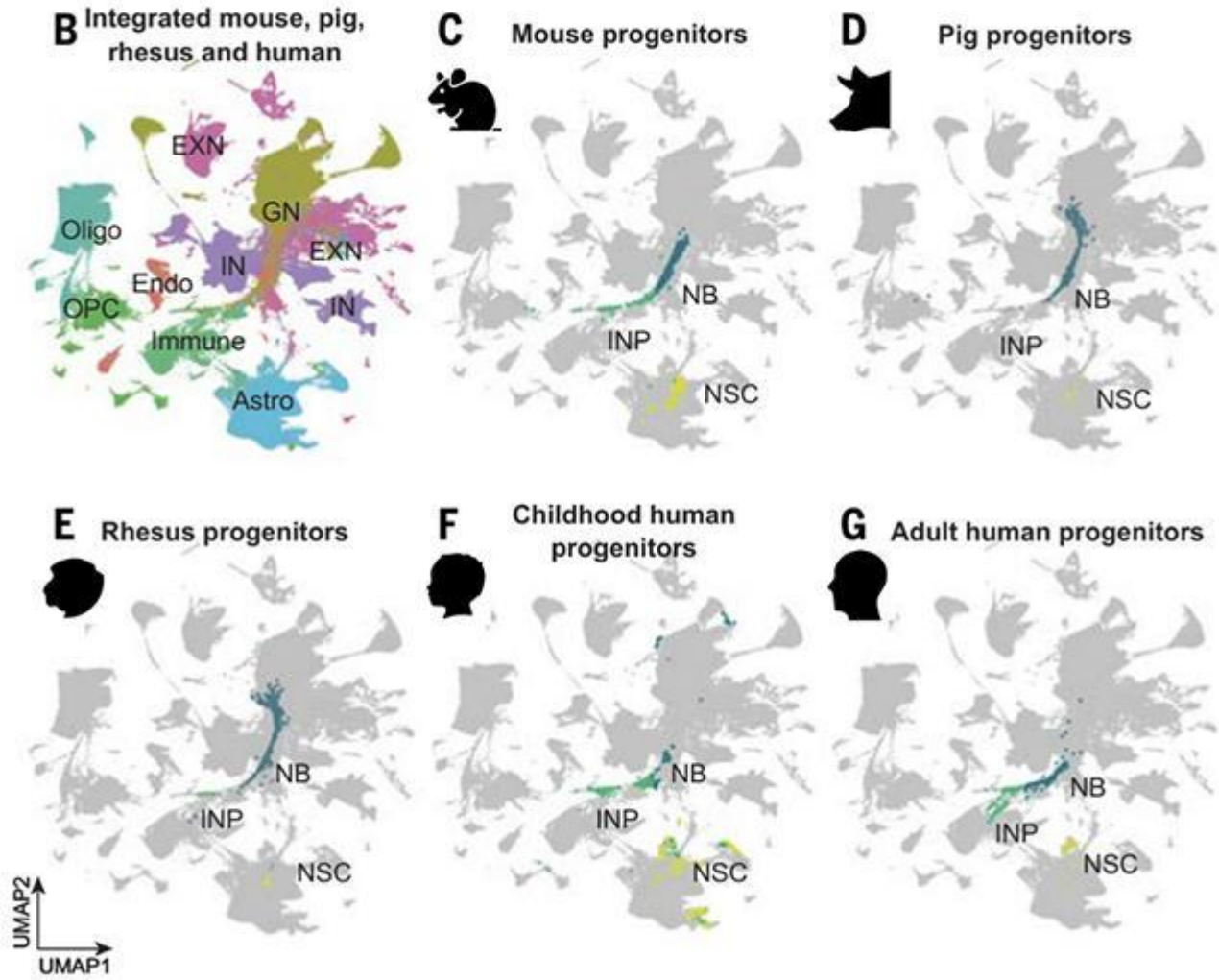
Previous studies have made the case for and against the existence of neurogenesis in hippocampus beyond childhood. A new study now offers some of the clearest evidence yet that this crucial memory-forming region does form fresh neurons well into adulthood.

The study is the work of researchers from the Karolinska Institute and the Chalmers University of Technology in Sweden, and looks specifically at the dentate gyrus section of the hippocampus, the part of the brain that acts as a key control center for emotions, learning, and storing episodic memories.

"This gives us an important piece of the puzzle in understanding how the human brain works and changes during life," says molecular biologist Jonas Frisén.

Confirmation that humans can form new neurons in the hippocampus through life (as several other animals can) would inform a whole host of other scientific investigations, from how adults learn new skills to what happens to the brain as it deteriorates in old age.

The team used RNA analysis to identify functions of brain cells in samples collected from people up to age 78, finding that some neurons were geared to function as neural progenitor cells (NPCs), which generate new nerve cells. The researchers also found similarities between human NPCs and those in mice, pigs, and monkeys.



Researchers compared neuron production between children, adults, and other animals. (Dumitru et al., Science , 2025)

Through a process of machine learning, the researchers could also group cells according to their development, from their initial 'blank slate' stem cell characterization to being an immature neuron in the process of dividing.

The results address questions raised by earlier studies (including one from some of the same researchers), which determined that new neurons were present in the human brain without being able to confirm exactly how they'd got there.

"We have now been able to identify these cells of origin, which confirms that there is an ongoing formation of neurons in the hippocampus of the adult brain," says Frisén.

By studying such a wide range of ages, the researchers confirmed neurogenesis keeps happening in the hippocampus throughout our adult lives – albeit at a slower rate, generally speaking, as we get older.

It's also important to note that the analysis revealed different rates of neurogenesis in different people. That might point to differences in brain plasticity that affect learning, personality, and disease risk, but that's something that future studies will need to look at.

One hypothesis is that certain brain conditions might be affected by how quickly fresh new neurons can be produced – some of the subjects in this study had a history of psychiatric or neurological diseases – but again this wasn't something that the researchers looked at directly, so follow-up studies will be needed.

"Our research may also have implications for the development of regenerative treatments that stimulate neurogenesis in neurodegenerative and psychiatric disorders," says Frisén.

Can a Nap Boost Brain Health?

Sleep Aging Well Aging and Sleep Age-Related Depression, Mood and Stress

Are you feeling a little guilty about your daily, mid-afternoon snooze? Don’t. Research shows that catching a few ZZZs after lunch can be good for your brain. But keep in mind that the length of your nap matters.

While a 30- to 90-minute nap in older adults appears to have brain benefits, anything longer than an hour and a half may create problems with cognition, the ability to think and form memories, according to the study published in the *Journal of the American Geriatrics Society*.

“I consider napping to be a good thing, but it needs to be taken in the context of the person and his or her own sleep cycles and body,” says Charlene Gamaldo, M.D., medical director of Johns Hopkins Sleep Disorders Center. For older people, as the study showed, longer naps tend to interfere with cognition, she says.

Napping for a Better Brain

Researchers looked at data from 2,974 people in China ages 65 and older. Nearly 60 percent of participants reported napping after lunch for about an hour.

Scientists found that people who napped for 30 to 90 minutes had better word recall – which is a sign of good memory – than people who did not nap or who napped for longer than 90 minutes. People who napped for that golden 30 to 90 minutes were also better at figure drawing, another sign of good cognition.

One theory explaining poor cognition in those who take longer naps: Resting more during the day may be a sign of poor quality nighttime sleep, according to Gamaldo. “In the study, naps longer than 90 minutes could have been called ‘a second sleep.’” This poor quality nighttime sleep – the kind that requires extra-long napping during the day – can lead to cognitive problems, she adds.

TRY ITTake an Afternoon Cat Nap

Research says that the best time for older adults to take to nap is between 1 and 4 p.m. because of their sleep-wake cycles, says Charlene Gamaldo, M.D., medical director of Johns Hopkins Sleep Disorders Center. “Napping this time of day will provide you with the most bang for your buck,” she says.

Ideally, the nap should last between 20 and 40 minutes to avoid feeling groggy immediately after you wake up. “A quick cat nap should be restorative,” she says. Shorter naps also ensure you don’t have trouble falling asleep at night.

More Problems with Longer Naps

Longer naps can pose a couple of other problems, says Gamaldo, including:

1. **Temporary grogginess**: People who take longer naps may feel groggy immediately after they wake up, says Gamaldo. “Because they are sleeping longer, they may wake up from a deeper stage of sleep, which occurs later in the cycle, and feel fuzzy headed,” she says.

2. **Inability to sleep at night**: Gamaldo has seen patients who take long naps during the day have insomnia at night. “You might want to think about limiting your napping if you’re having problems with insomnia, or it’s taking you more than 30 minutes to fall asleep at bedtime.”

A Fine Balance

Overall, studies show that people who sleep too much or too little may have poor health and even a shorter life span. Consequently, “people need to get the right quantity and quality of rest,” says Gamaldo.

Scientists Beamed Light Right Through a Man's Head For The First Time

Light behind a human head

Scientists have developed a new technique for non-invasive brain imaging – and it involves shining light all the way through the head, from one side to the other.

Currently the best portable, low-cost method for monitoring the brain is functional near-infrared spectroscopy (fNIRS). Unfortunately, this can only

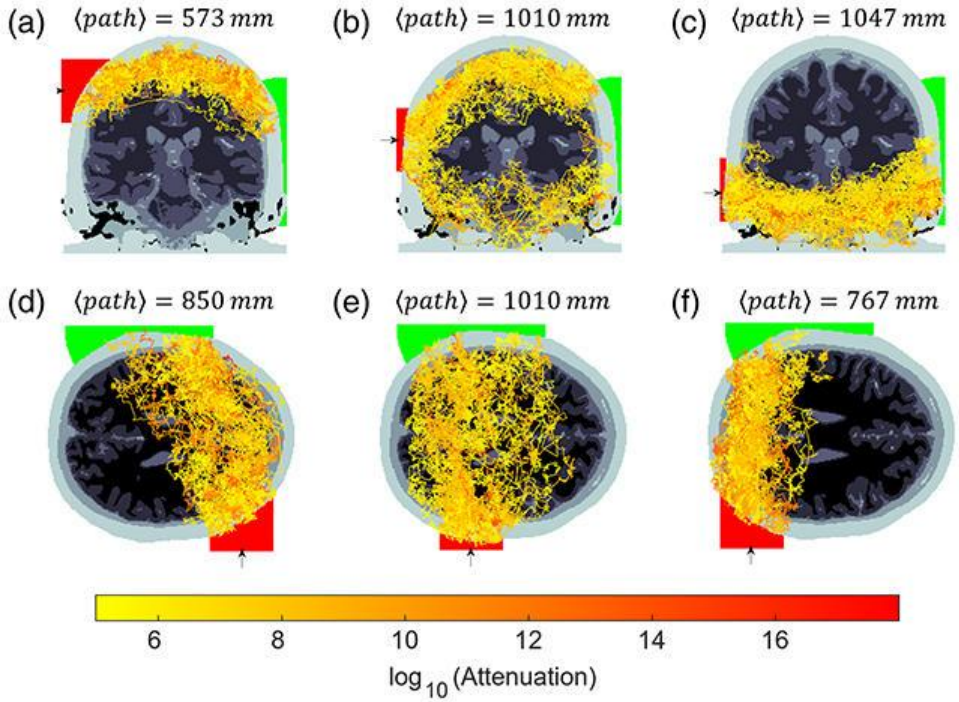
penetrate a few centimeters down, meaning bigger, bulkier MRI machines are needed to probe deeper layers of the brain.

A new method, developed by a team from the University of Glasgow in Scotland, expands the sensitivity of fNIRS to shine light all the way through the complex combinations of bone, neurons, and tissue that make up our heads.

Doing so required a few tweaks: the researchers increased the strength of the near-infrared laser (within safe boundaries, of course), while also putting in place a more comprehensive collection setup.

Even with these adjustments, only a small trickle of photons made it from one side of the head to the other during experiments. However, it's a promising start for portable imaging methods that go deeper, giving us crucial insight into what's happening inside our skulls without opening them up.

"These findings uncover the potential to extend non-invasive light based on brain imaging technologies to the tomography of critical biomarkers deep in the adult human head," write the researchers in their published paper.



Measured light matched up with computer models. (Radford et al., Neurophotonics , 2025)

There are quite a number of caveats to mention here. The process was only successful with one out of eight study participants: a man with fair skin and no hair on his head. It needs a very specific setup, and an extended scanning time – around 30 minutes.

Those limitations are all acknowledged by the researchers, but they sacrificed certain variables (such as speed) to try and prove that it was possible to get light all the way through a human head via fNIRS – and they succeeded.

Computer models based on detailed 3D head scans were used to predict the movement of photons through the skull. These matched up closely with the actual light collected, adding further credibility to the results.

What's more, the research also found that light didn't scatter at random through the head, but rather followed preferred paths – including through parts that were more transparent, like those filled with cerebrospinal fluid. That knowledge could help brain scans be better targeted in the future.

"Different source positions on the head can then selectively isolate and probe deep regions of the brain," write the researchers.

The advantages of fNIRS are that it's a relatively inexpensive and compact technology. Imagine scans for strokes, brain injuries, and tumors that are more accessible for a wider range of people.

As future imaging devices are developed, this research should prove useful for techniques that go deeper into the brain – even if it might be a while before we can get light through the entire head in a timeframe that's practically useful.

We know that brain scans have tremendous value in everything from understanding adolescence in youngsters to treating disease towards the end of our lives, so there's a huge amount of potential here.

"Optical modalities for noninvasive imaging of the human brain hold promise to fill the technology gap between cheap and portable devices such as

electroencephalography (EEG) and expensive high-resolution instruments such as functional magnetic resonance imaging (fMRI)," write the researchers.

The research has been published in *Neurophotonics*.

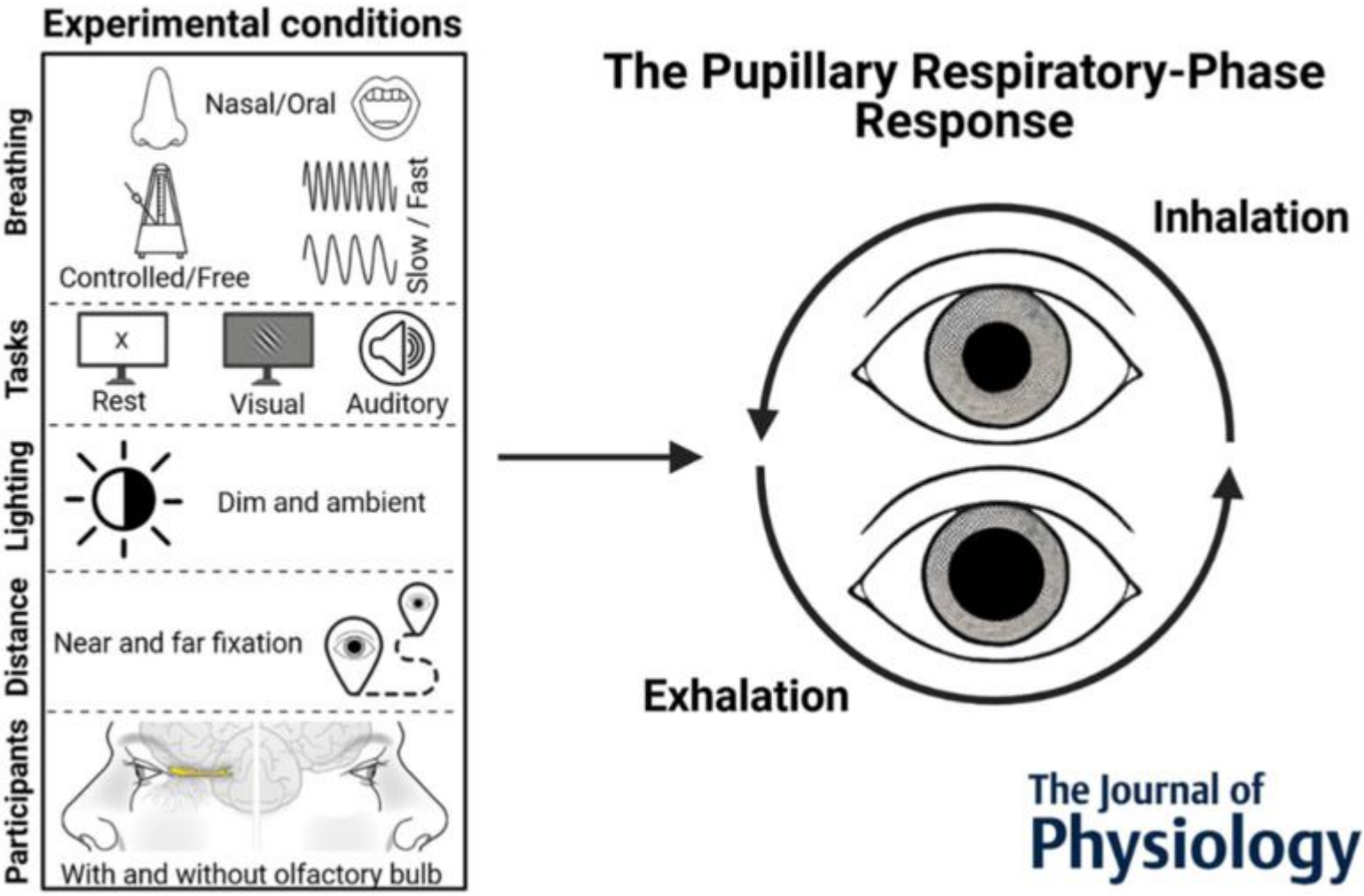
Scientists discover a critical link between breathing and vision

New research reveals that the way you breathe can change the size of your pupils, subtly shaping how you see the world. (CREDIT: CC BY-SA 4.0)© The Brighter Side of News

For over a century, scientists believed that light, focus distance, and cognitive effort were the main forces behind changes in pupil size. But a new discovery adds breathing to that list. Researchers from Karolinska Institutet in Sweden have found that the simple act of breathing subtly shapes how our pupils behave.

The study, published in The Journal of Physiology, reveals a striking pattern: pupils shrink during inhalation and expand during exhalation. This rhythmic shift points to a basic biological process that might influence not only vision but also how we experience the world around us.

Much like a camera's aperture, the pupil adjusts the amount of light reaching the eye. When it narrows or widens, it changes the way we see—sharpening fine details or making faint objects easier to spot. Now, with breathing added to the equation, it appears our vision quietly fluctuates throughout every breath we take.



Abstract figure. Across five experiments including 203 participants and a wide range of experimental conditions researchers demonstrate that pupil size fluctuates in a systematic manner over the course of the breathing cycle. (CREDIT: The Journal of Physiology)© The Brighter Side of News

"This mechanism is unique in that it is cyclical, ever-present, and requires no external stimulus," says Artin Arshamian, associate professor at the Department of Clinical Neuroscience at Karolinska Institutet. "Since breathing affects brain activity and cognitive functions, the discovery may contribute to a better understanding of how our vision and attention are regulated."

The Brain, Breathing and Visual Focus

The new findings build on a growing body of research showing that breathing does more than supply oxygen. It also generates rhythmic electrical patterns, known as neural oscillations, that sweep across the brain and shape how we think and perceive.

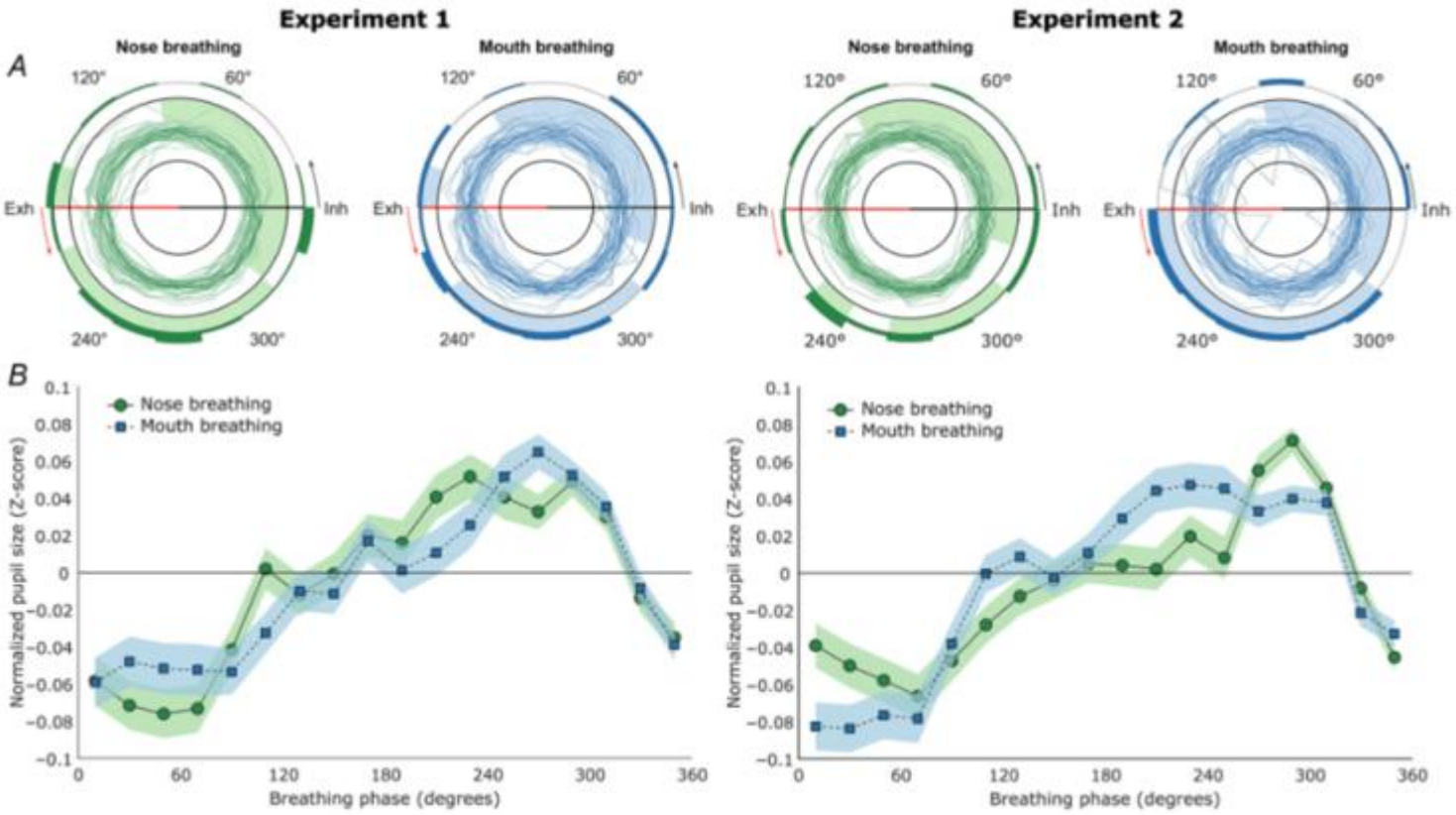
These oscillations are born deep within the brainstem, in a cluster of neurons called the preBötzinger complex, which controls breathing rhythms. They also emerge in the olfactory bulb, triggered when air moves through the nose, linking breath directly to brain function.

Animal studies have shown that breathing-related brain rhythms help synchronize sensory and motor behaviors such as sniffing, whisking, and head movements. Likewise, the control of pupil size plays a critical role in processing visual information, adjusting how much the brain can detect and respond to.

Until now, though, clear proof connecting breathing to pupil changes had been missing. Earlier studies struggled with small sample sizes and inconsistent methods, leaving the link between respiration and vision largely unexplored—until this discovery.

To clarify this connection, the research team conducted five carefully controlled experiments with over 200 participants. Their findings confirmed that breathing consistently influenced pupil size across various conditions, whether participants were breathing quickly or slowly, through the nose or mouth, in bright or dim lighting, at rest, or engaged in visual tasks.

One of the most striking results was that the pupil fluctuations occurred even in individuals born without an olfactory bulb, a brain structure typically associated with nasal breathing. This suggests that the brainstem alone may regulate the effect, highlighting its deep evolutionary roots.



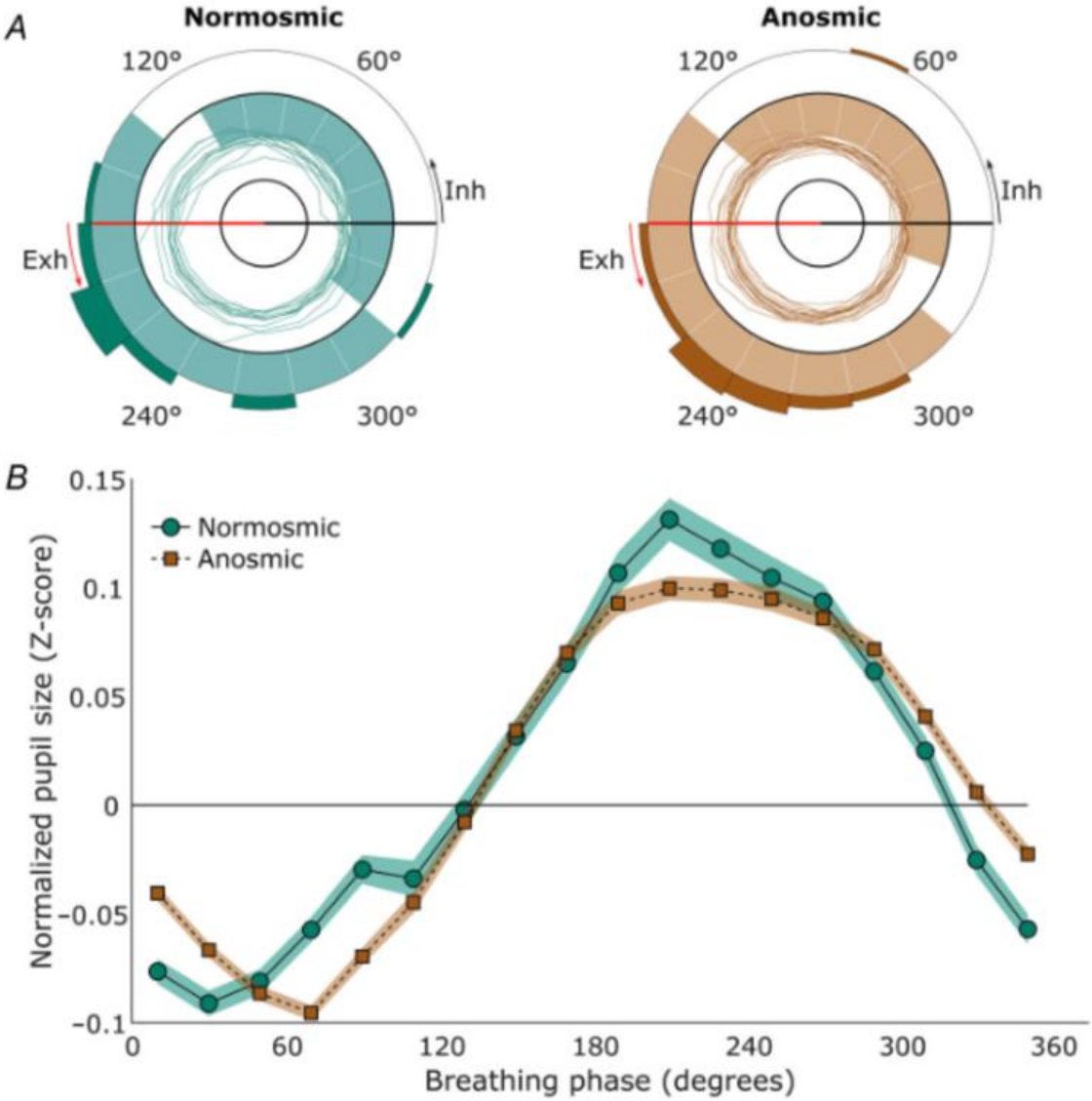
Polar plots of participants' pupil sizes over the course of the breathing cycle. 0° (Inh) marks the onset of inhalation, 90° marks peak inhalation, 180° (Exh) marks the onset of exhalation, and 270° marks peak exhalation. (CREDIT: The Journal of Physiology)© The Brighter Side of News

How Pupil Changes May Shape Perception

The study raises intriguing possibilities about how vision shifts in response to breathing. Pupil size directly affects how light enters the eye, influencing visual acuity. A smaller pupil, like a camera lens set to a narrow aperture, enhances sharpness and depth of field, making it easier to see fine details. A larger pupil, by contrast, allows more light to enter, improving sensitivity to dim or distant objects.

“Our results suggest that our vision may switch between optimizing for distinguishing small details when we inhale and detecting faint objects when we exhale, all within a single breathing cycle,” says Martin Schaefer, a postdoctoral researcher at Karolinska Institutet and the study’s first author.

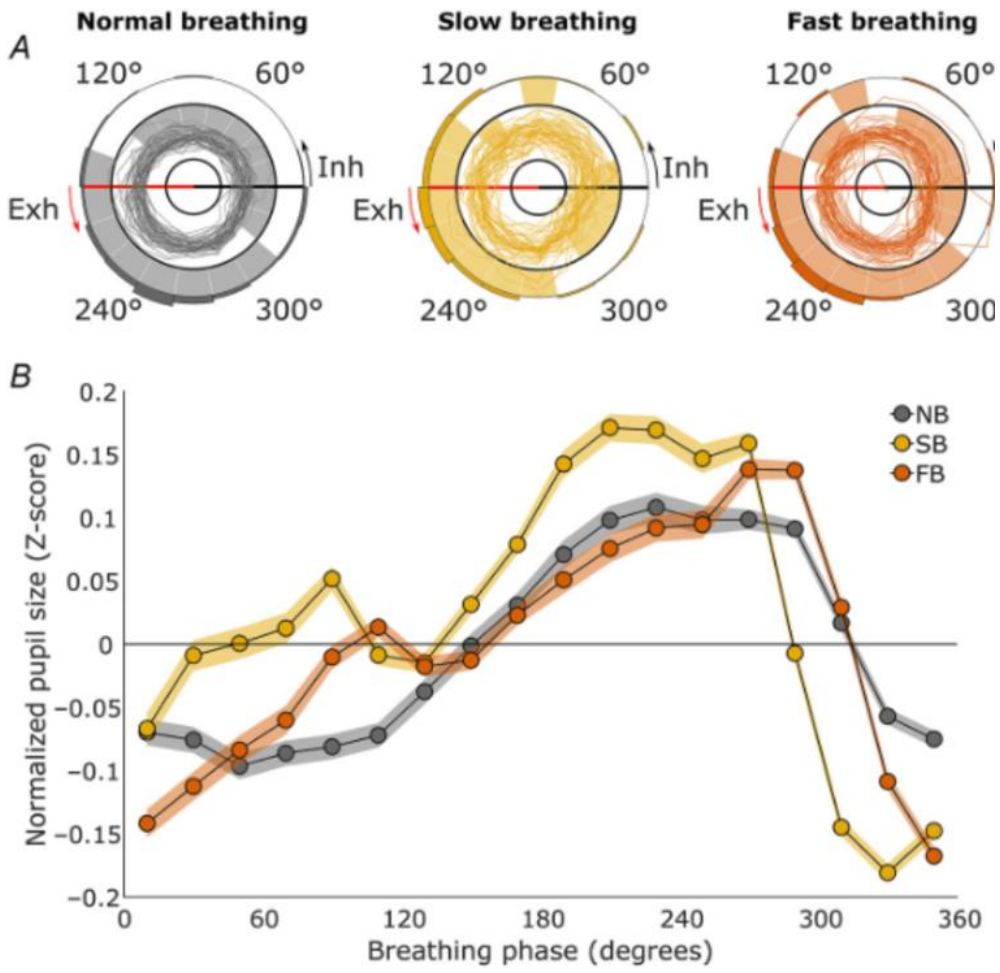
If this effect is strong enough to impact perception, it could have significant implications for daily activities. Tasks requiring high visual precision, such as reading or threading a needle, might be easier when inhaling. Meanwhile, scanning for movement in low light, such as spotting a shadow at night, might be enhanced during exhalation.



Pupil size in participants with and without olfactory bulbs. (CREDIT: The Journal of Physiology)© The Brighter Side of News

Beyond its effects on vision, the link between respiration and pupil size may have medical applications. The autonomic nervous system, which controls involuntary bodily functions, regulates both breathing and pupil response. Abnormalities in this system can signal neurological disorders. “One potential application is new methods to diagnose or treat neurological conditions such as Parkinson's disease, where damage to pupil function is an early sign of the disease,” says Arshamian. “This is something we want to explore in the future.”

Pupil measurements are already used in clinical settings to assess brain function, detect brain injuries, and monitor states of consciousness. If respiration-induced pupil changes serve as an additional diagnostic marker, they could offer a new, non-invasive way to detect early signs of neurological disease.



Pupil size during paced breathing. (CREDIT: The Journal of Physiology)© The Brighter Side of News

Future research will determine how this discovery might be applied in medical diagnostics and whether breathing techniques could be used to modulate attention and perception.

While much remains to be explored, this study offers a new perspective on how breath, brain, and vision are interconnected.

Revolutionary brain implant converts thoughts to text with over 90% accuracy

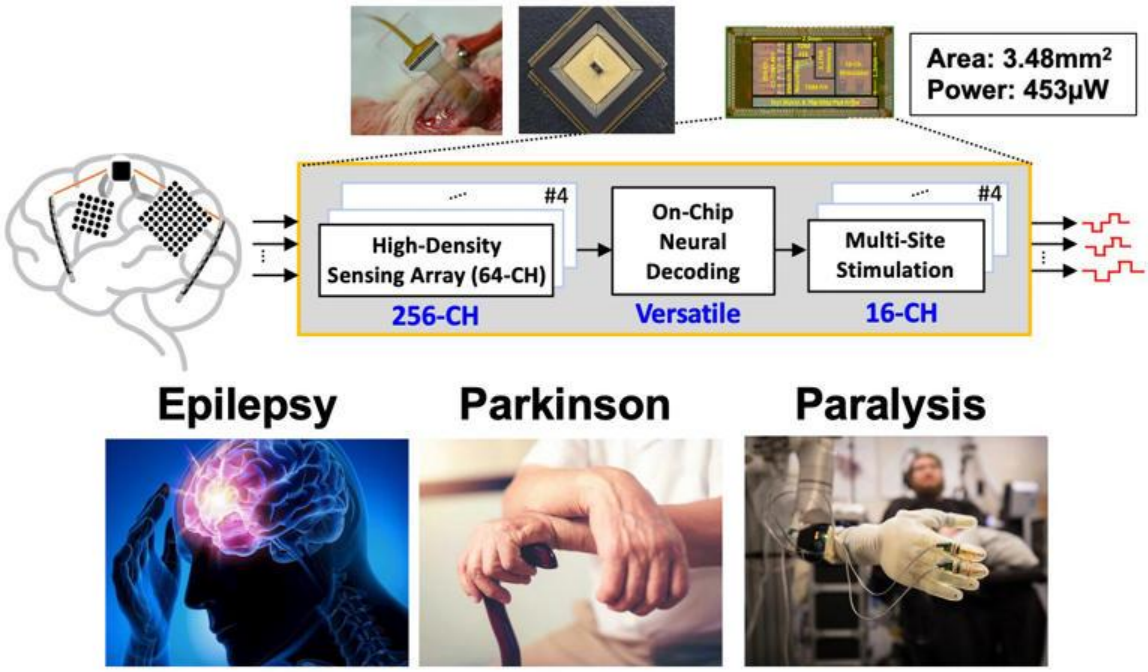
EPFL introduces a groundbreaking miniaturized brain-machine interface (MiBMI), enabling accurate, real-time translation of thoughts into readable text. (CREDIT: Pixabay/AI generated)© The Brighter Side of News

Brain-machine interfaces (BMIs) are becoming lifelines for people facing severe motor impairments. For many individuals with conditions like amyotrophic lateral sclerosis (ALS) or spinal cord injuries, BMIs offer hope. Yet, traditional systems remain bulky and consume too much power for everyday use, limiting their practicality.

Now, researchers at EPFL have introduced a groundbreaking solution: a Miniaturized Brain-Machine Interface (MiBMI). This compact, energy-efficient innovation stands poised to redefine what's possible in neurotechnology. Unlike its predecessors, MiBMI fits onto just two tiny silicon chips, covering an area smaller than a fingernail. Such compactness means these chips could easily be implanted into patients, significantly enhancing their quality of life.

Transforming Thoughts into Text

MiBMI works by capturing neural signals when you think about writing. Electrodes implanted within the brain detect the specific patterns of activity tied to imagined handwriting. The system then decodes this activity into actual text displayed on a screen in real-time. It's an extraordinary leap forward, offering individuals who cannot speak or move a powerful new communication tool.



The SoC is versatile and can be used in different applications including epilepsy, movement disorders, and motor decoding in BCIs.© The Brighter Side of News

The core of this innovation is a sophisticated yet simple decoding method. The system identifies unique markers known as distinctive neural codes (DNCs). These markers drastically simplify the decoding process, focusing only on essential brain activity.

By reducing complex neural signals into smaller, manageable data units, the MiBMI achieves rapid, accurate translation of thought to text. According to Mohammed Ali Shaeri, lead author from EPFL, "the chip processed data from previous live recordings with an impressive 91% accuracy in converting handwriting activity into text."

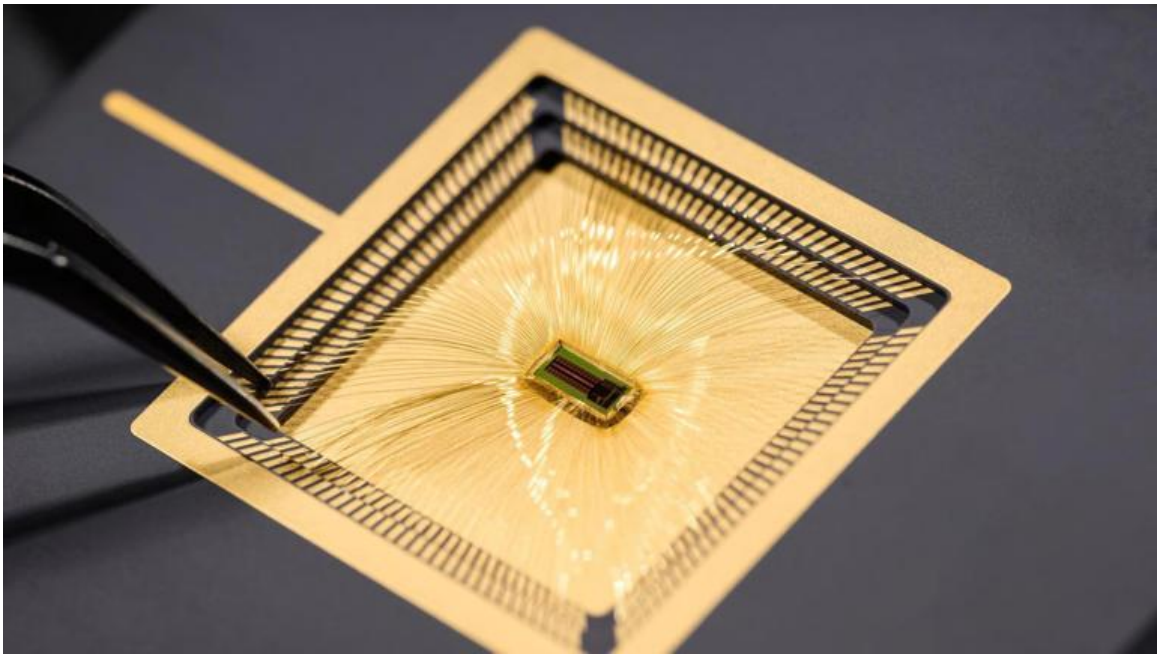
Currently, MiBMI decodes up to 31 distinct characters, surpassing any other integrated system developed so far. However, Shaeri notes the potential extends even further, suggesting, "We are confident we can decode up to 100 characters. But a handwriting dataset with more characters isn't available yet."

Efficiency in a Tiny Package

Aside from accuracy, MiBMI's compact size is one of its greatest strengths. The entire chipset occupies only 2.46 mm^2 and consumes less than one milliwatt of power, a huge improvement over earlier models. This remarkable miniaturization means MiBMI can be fully implanted, enhancing patient safety and comfort.

Mahsa Shoaran, director of EPFL's Integrated Neurotechnologies Laboratory (INL), emphasizes its revolutionary potential. "MiBMI allows us to convert intricate neural activity into readable text with high accuracy and low power consumption," Shoaran explains. "This advancement brings us closer to practical, implantable solutions that can significantly enhance communication abilities for individuals with severe motor impairments."

Such breakthroughs are essential since traditional BMIs have relied heavily on external computers to process neural signals. MiBMI's real-time recording and processing capabilities eliminate this cumbersome step, dramatically improving its usability and convenience.



Researchers from EPFL have developed a next-generation miniaturized brain-machine interface capable of direct brain-to-text communication on tiny silicon chips. (CREDIT: EPFL)© The Brighter Side of News

Smarter and Faster Technology

MiBMI is built around a clever use of machine learning, specifically a streamlined form called linear discriminant analysis (LDA). This method makes decoding

quicker, uses significantly less memory, and reduces complexity by hundreds of times compared to conventional techniques.

For example, MiBMI's innovative approach achieves a memory reduction of around 100 times and computational simplification by approximately 320 times.

These improvements are crucial for practical use, making the device fast and efficient enough to process complex neural information almost instantly. Such efficiency opens possibilities beyond simple motor tasks. "We are exploring various applications beyond handwriting recognition," says Shoaran. "Collaborations are underway to test speech decoding and even precise movement control."

Miniaturized Brain-Machine Interface (MiBMI). (CREDIT: 2024 EPFL / Lundi13)© The Brighter Side of News

Broadening Possibilities

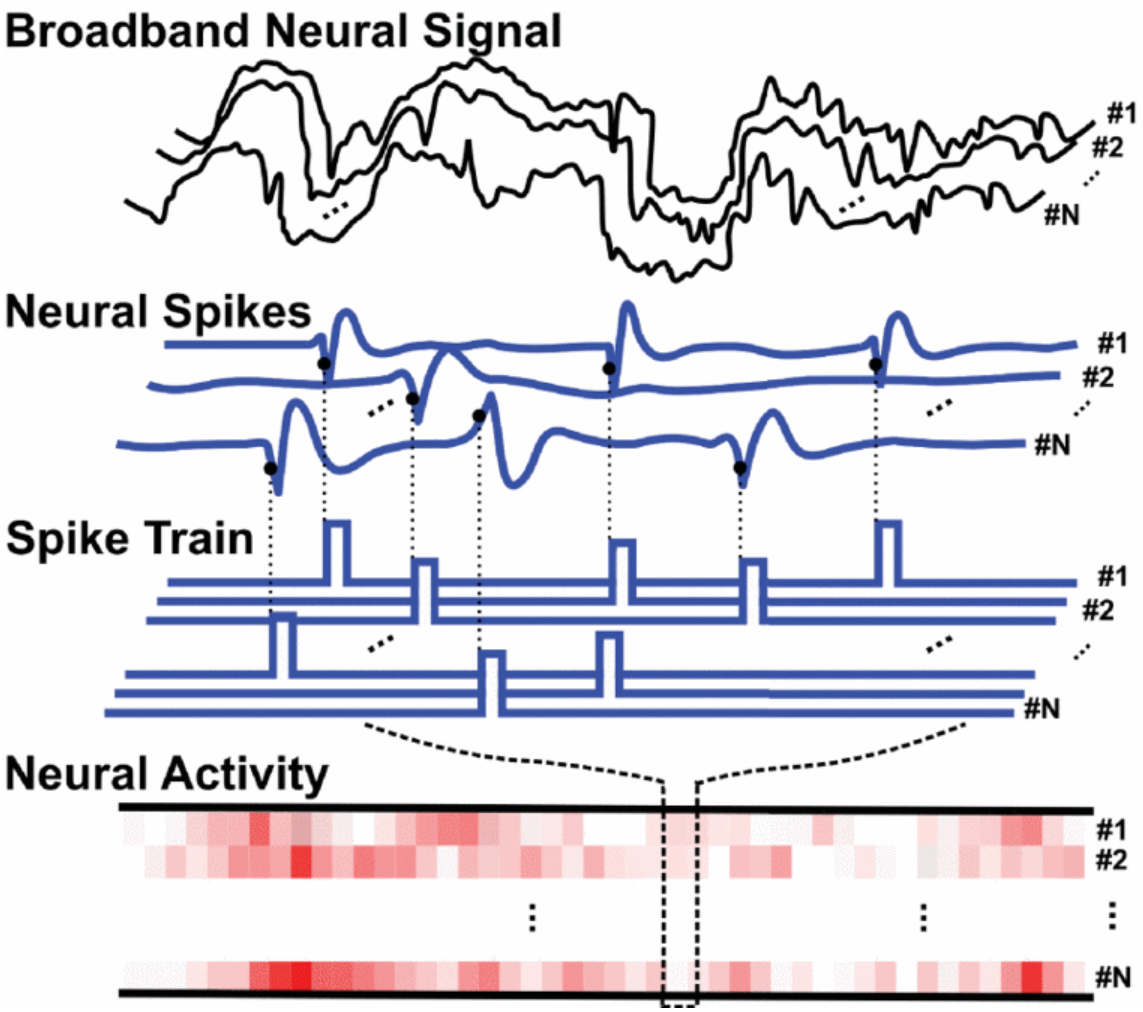
The versatility of MiBMI is another compelling feature. The system has already demonstrated its ability to decode diverse neural responses, such as recognizing different acoustic signals in experiments with rats, achieving 87% accuracy. This flexibility shows the potential for broader medical applications, including

managing epilepsy, monitoring movement disorders, and enhancing communication through speech decoding.

Moreover, MiBMI integrates advanced machine learning into its tiny structure. Its embedded algorithms allow the chipset to quickly learn and recognize patterns from neural activity. Such integration ensures the system remains adaptable and effective for individual users, significantly shortening the learning curve associated with BMI systems.

The collaborative spirit at EPFL amplifies this technology's potential. Shoaran and Shaeri have joined forces with prominent researchers like Grégoire Courtine, Silvestro Micera, Stéphanie Lacour, and David Atienza. These collaborations promise to propel MiBMI into various medical and neurological contexts, further enhancing its real-world applications.

Shoaran remains optimistic, stating, "Our goal is to develop a versatile BMI tailored to various neurological disorders, providing broader solutions for patients."



N-channel neural signal at various processing steps: broadband neural signals, neuronal spikes, binary spike trains indicating detected or sorted spikes, and neural activity derived from smoothing the spike rates. (CREDIT: EPFL)© The Brighter Side of News

As BMIs continue evolving, MiBMI stands at the forefront, offering new hope for those with limited movement or communication abilities. By making these devices smaller, smarter, and more efficient, researchers at EPFL are opening doors once thought impossible to reach. Soon, a world where thought alone enables seamless communication might become reality, offering renewed independence to those who need it most.

Research findings are available online in IEEE Journal of Solid-State Circuits.

How the brain synchronizes itself with rhythmic stimuli

Transcranial alternating current stimulation (tACS): Every individual responded most strongly to a different stimulation frequency. Credit: MPI for Empirical Aesthetics / F. Bernoully

Our brain is adept at synchronizing with rhythmic sounds, whether it's the beat of a song or the steady patter of rain. This ability helps us recognize and process sounds more effectively.

A research team led by the Max Planck Institute for Empirical Aesthetics (MPIEA) in Frankfurt am Main has shown that stimulation with weak electrical currents, known as transcranial alternating current stimulation (tACS), can influence this ability. The new study is published in the journal *PLOS Biology*.

The study builds on previous work showing that tACS can either enhance or suppress brain rhythms depending on how it's timed with incoming sound. In order to investigate the interaction between electrical stimulation and brain rhythms, 50 participants took part in three experiments where they listened to noisy sounds and were asked to identify short, barely perceptible pauses. The researchers then transmitted electrical rhythms to the participants' brains via electrodes placed on their scalps several times to see how this influenced their brain activity.

The results showed that when natural rhythmic sounds were present, the brain primarily followed these stimuli with clear behavioral consequences. The degree of synchronization varied depending on how dominant the rhythms were.

However, the electrical current had little influence on this. Only when the sounds had hardly any rhythm or were barely perceptible was the influence of electrical stimulation clearly noticeable. Interestingly, the effect varied greatly from person to person, with each individual responding most strongly to a different stimulation frequency.

"The study shows how the brain responds to stimulation frequencies on an individual level. Weak currents can influence hearing, but only if strong rhythmic

acoustic stimuli are not present to interfere. For it to be effective, the frequency of the current must also be adjusted for each individual," explains lead author Yuranny Cabral-Calderin from MPIEA.

This research opens new possibilities for personalized brain stimulation techniques aimed at enhancing attention, perception, and potentially supporting rehabilitation. First, it demonstrates that rhythmic auditory stimulation can reliably modulate brain activity and influence behavior, highlighting its potential as a low-cost, non-invasive neuromodulation approach.

Second, the findings suggest that therapeutic applications of electrical brain stimulation to support auditory processing should be individually tailored—adjusting stimulation parameters to align with each person's endogenous brain rhythms for maximal effectiveness.

More information: Yuranny Cabral-Calderin et al, Sensory stimuli dominate over rhythmic electrical stimulation in modulating behavior, *PLOS Biology* (2025). DOI: 10.1371/journal.pbio.3003180

Provided by Max Planck Society

Discovery of a second learning system in the brain

A team of researchers from University College London has just unveiled a second learning system in the brain that sheds light on habit formation.

Scientists at the Sainsbury Wellcome Centre have identified two distinct ways of learning through trial and error. This discovery, published in *Nature*, could change our understanding of compulsive behaviors and addictions.

Discovery of a second learning system in the brain

They revealed a never-before-seen signal produced by dopamine, called "action prediction error" (APE). Unlike the usual signal that evaluates reward, APE measures the frequency of repeated actions. Thanks to these two systems, the

brain can learn either by favoring what brings the most reward or by repeating what is most frequent.

The experiments used an auditory test to observe neurons linked to mouse movement. Results show that mice without the rear part of the striatum are unable to reach a high performance level. This means APE takes over during advanced learning phases.

This discovery opens interesting perspectives for treating addictions. By acting on the habit system, harmful behaviors could be replaced with healthier ones. The implications for Parkinson's disease are also significant, particularly in explaining why some automatic movements are affected.

Scientists now want to understand how the two learning systems interact. Better knowledge of these mechanisms could lead to new therapies for behavioral disorders and neurodegenerative diseases.

How does dopamine influence our habits?

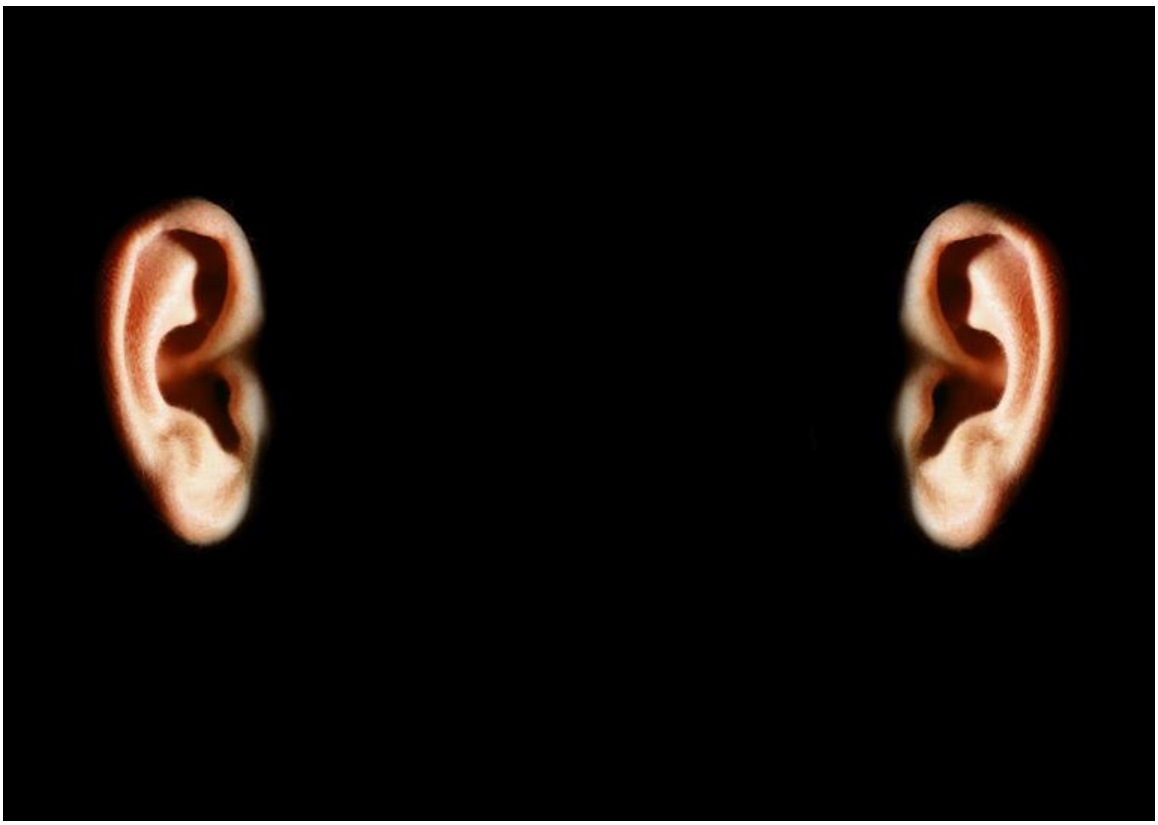
Dopamine is a key molecule in the brain, linked to pleasure and motivation. It plays an essential role in habit formation by signaling reward prediction errors and action errors.

Researchers discovered it acts differently depending on whether it's an expected reward or a repeated action. This difference explains why some habits are so hard to change, even when they're no longer rewarding.

These advances help better understand addiction mechanisms. By precisely targeting dopaminergic signals, new treatments could be developed to change behaviors.

Source: Nature

Your left and right brain hear language differently – a neuroscientist explains how



How you process language is influenced by how each side of your brain developed in early life.© Peter Dazeley/The Image Bank via Getty Images

Some of the most complex cognitive functions are possible because different sides of your brain control them. Chief among them is speech perception, the ability to interpret language. In people, the speech perception process is typically dominated by the left hemisphere.

Your brain breaks apart fleeting streams of acoustic information into parallel channels – linguistic, emotional and musical – and acts as a biological multicore processor. Although scientists have recognized this division of cognitive labor for over 160 years, the mechanisms underpinning it remain poorly understood.

Researchers know that distinct subgroups of neurons must be tuned to different frequencies and timing of sound. In recent decades, studies on animal

models, especially in rodents, have confirmed that splitting sound processing across the brain is not uniquely human, opening the door to more closely dissecting how this occurs.

Yet a central puzzle persists: What makes near-identical regions in opposite hemispheres of the brain process different types of information?

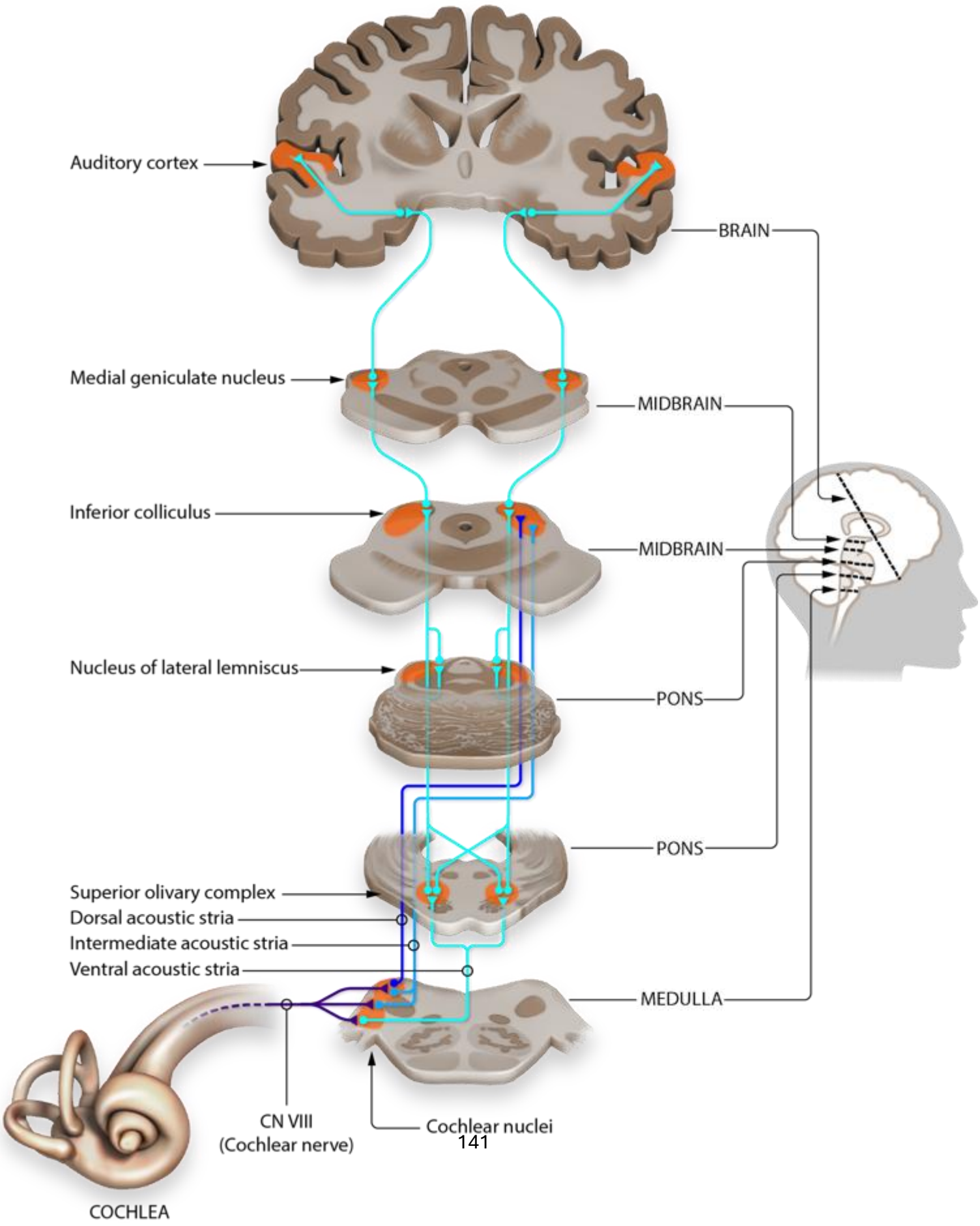
Answering that question promises broader insight into how experience sculpts neural circuits during critical periods of early development, and why that process is disrupted in neurodevelopmental disorders.

Timing is everything

Sensory processing of sounds begins in the cochlea, a part of the inner ear where sound frequencies are converted into electricity and forwarded to the auditory cortex of the brain. Researchers believe that the division of labor across brain hemispheres required to recognize sound patterns begins in this region.

For more than a decade, my work as a neuroscientist has focused on the auditory cortex. My lab has shown that mice process sound differently in the left and right hemispheres of their brains, and we have worked to tease apart the underlying circuitry.

For example, we've found the left side of the brain has more focused, specialized connections that may help detect key features of speech, such as distinguishing one word from another. Meanwhile, the right side is more broadly connected, suited for processing melodies and the intonation of speech.


Auditory cortex
BRAIN
Medial geniculate nucleus
MIDBRAIN
Inferior colliculus
MIDBRAIN
Nucleus of lateral lemniscus
PONS
PONS
Superior olivary complex
Dorsal acoustic stria
Intermediate acoustic stria
Ventral acoustic stria
MEDULLA
CN VIII
(Cochlear nerve)
Cochlear nuclei
COCHLEA

Sound information moves through the cochlea to the brain.© Jonathan E. Peelle

We tackled the question of how these left-right differences in hearing develop in our latest work, and our results underscore the adage that timing is everything.

We tracked how neural circuits in the left and right auditory cortex develop from early life to adulthood. To do this, we recorded electrical signals in mouse brains to observe how the auditory cortex matures and to see how sound experiences shape its structure.

Surprisingly, we found that the right hemisphere consistently outpaced the left in development, showing more rapid growth and refinement. This suggests there are critical windows of development – brief periods when the brain is especially adaptive and sensitive to environmental sound – specific to each hemisphere that occur at different times.

To test the consequences of this asynchrony, we exposed young mice to specific tones during these sensitive periods. In adulthood, we found that where sound is processed in their brains was permanently skewed. Animals that heard tones during the right hemisphere's earlier critical window had an overrepresentation of those frequencies mapped in the right auditory cortex.

Adding yet another layer of complexity, we found that these critical windows vary by sex. The right hemisphere critical window opens earlier in female mice, and the left hemisphere window opens just days later. In contrast, male mice had a very sensitive right hemisphere critical window, but no detectable window on the left. This points to the elusive role sex may play in brain plasticity.

Our findings provide a new way to understand how different hemispheres of the brain process sound and why this might vary for different people. They also provide evidence that parallel areas of the brain are not interchangeable: the brain can encode the same sound in radically different ways, depending on when it occurs and which hemisphere is primed to receive it.

Speech and neurodevelopment

The division of labor between brain hemispheres is a hallmark of many human cognitive functions, especially language. This is often disrupted in neuropsychiatric conditions such as autism and schizophrenia.

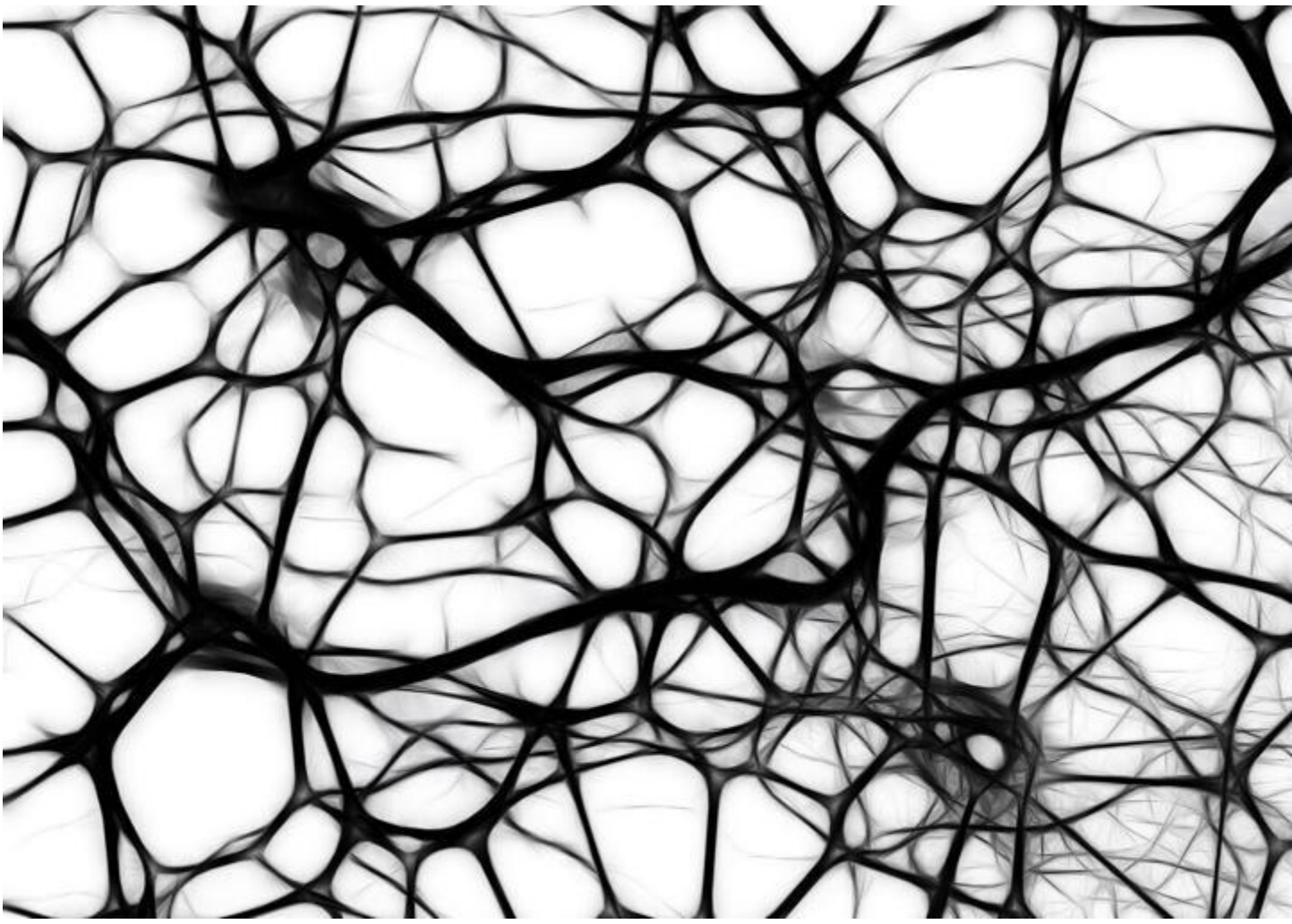
Reduced language information encoding in the left hemisphere is a strong indication of auditory hallucinations in schizophrenia. And a shift from left- to right-hemisphere language processing is characteristic of autism, where language development is often impaired.

Children with certain neurodevelopmental conditions may have trouble processing speech.© Towfiqu Ahamed/iStock via Getty Images Plus

Strikingly, the right hemisphere of people with autism seems to respond earlier to sound than the left hemisphere, echoing the accelerated right-side maturation we saw in our study on mice. Our findings suggest that this early dominance of the right hemisphere in encoding sound information might amplify its control of auditory processing, deepening the imbalance between hemispheres.

These insights deepen our understanding of how language-related areas in the brain typically develop and can help scientists design earlier and more targeted treatments to support early speech, especially for children with neurodevelopmental language disorders.

The brain's map of space: A new discovery about how our brains represent information



Credit: Pixabay/CC0 Public Domain© Provided by Medical Xpress

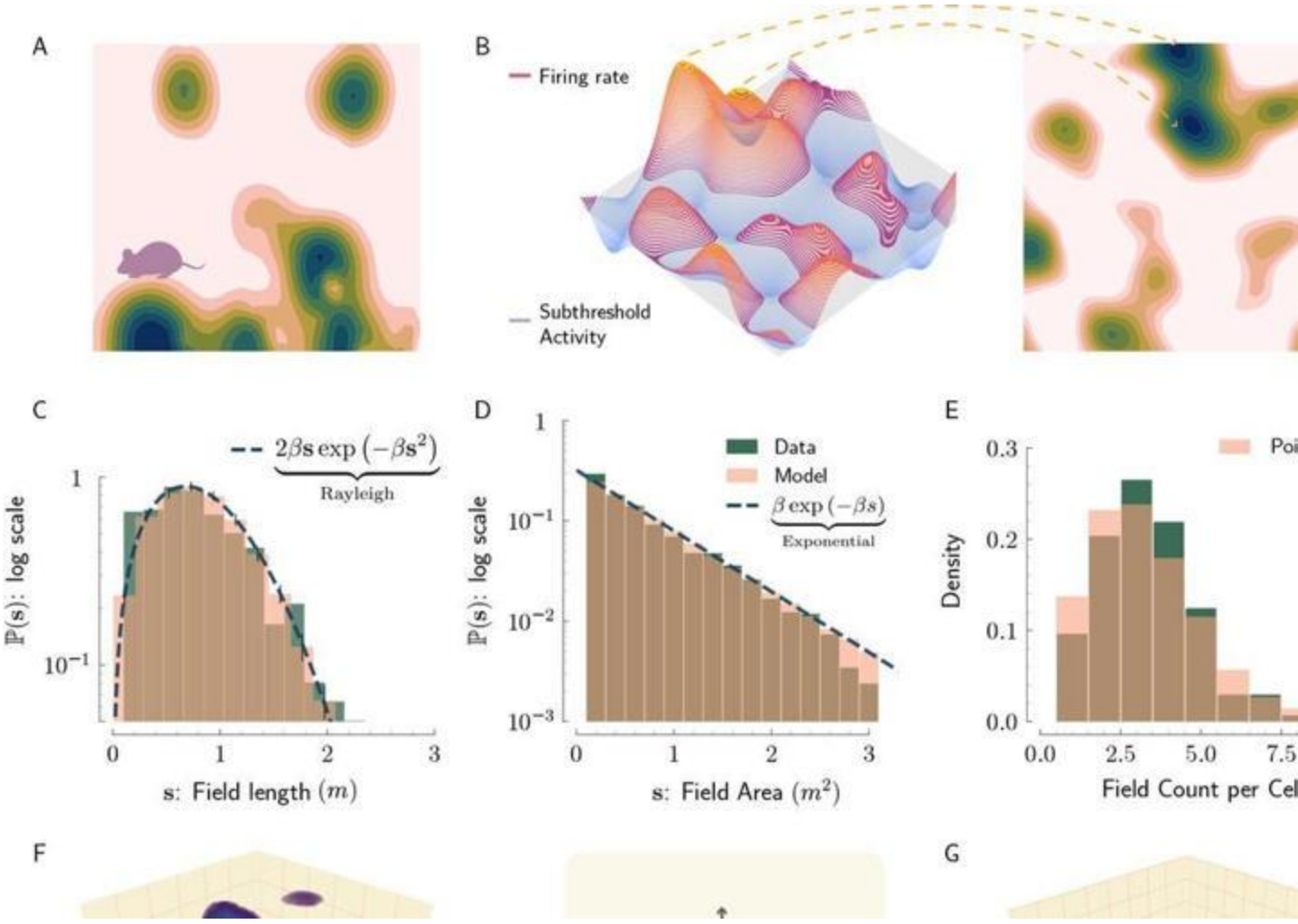
A new study led by Prof. Yoram Burak of the Edmond and Lily Safra Center for Brain Sciences and the Racah Institute of Physics at the Hebrew University of Jerusalem unveils a unifying mathematical framework to explain how "place cells" in the hippocampus encode spatial information across diverse species and environments.

The study is published in the journal *Neuron*.

Place cells are specialized neurons in the hippocampus that help animals navigate by creating firing patterns that encode locations within the animals' surroundings. Traditionally, these cells were thought to fire in single, compact regions of space with a stereotypical symmetric shape.

However, recent research has revealed that in larger environments, these cells display much more complex and irregular patterns of activity, firing in multiple locations with varied shapes and sizes.

Prof. Burak's team has found that a remarkably simple yet powerful mathematical model explains the irregular firing patterns of place cells in large environments. The model is based on the concept of "Gaussian Processes", a class of random functions that play an important role in diverse natural phenomena ranging from cosmology to oceanography.



Field arrangements of place fields in 2d and 3d spaces are explained by the thresholded Gaussian process model. Credit: Nischal Mainali

In the model, firing regions of place cells emerge by marking regions of space in which a random Gaussian process crosses a certain threshold. Using this simple model, the researchers showed that the activity of place cells in bats and rodents across 1D, 2D, and 3D spaces follows universal principles.

Related video: Zero-G Neurological Mysteries: How Space Rewires Animal Brains (Animals Around The Globe)

These findings imply that these patterns arise from largely random inputs to the hippocampus, challenging the idea that the brain relies on precise organization for its spatial map.

"Our findings suggest that randomness, rather than specific design, governs the synaptic organization of inputs to CA1 neurons in the hippocampus," explains Nischal Mainali, a student at the Hebrew University and one of the authors of the study.

This perspective challenges long-held assumptions about the structure of neural circuits and opens new avenues for understanding spatial cognition.

The model also makes precise testable predictions about the arrangements of place cell firing fields, and their geometry, which were verified by re-examining recordings of place cell activity, collected in previous experiments from bats, mice, and rats that navigated in diverse environments.

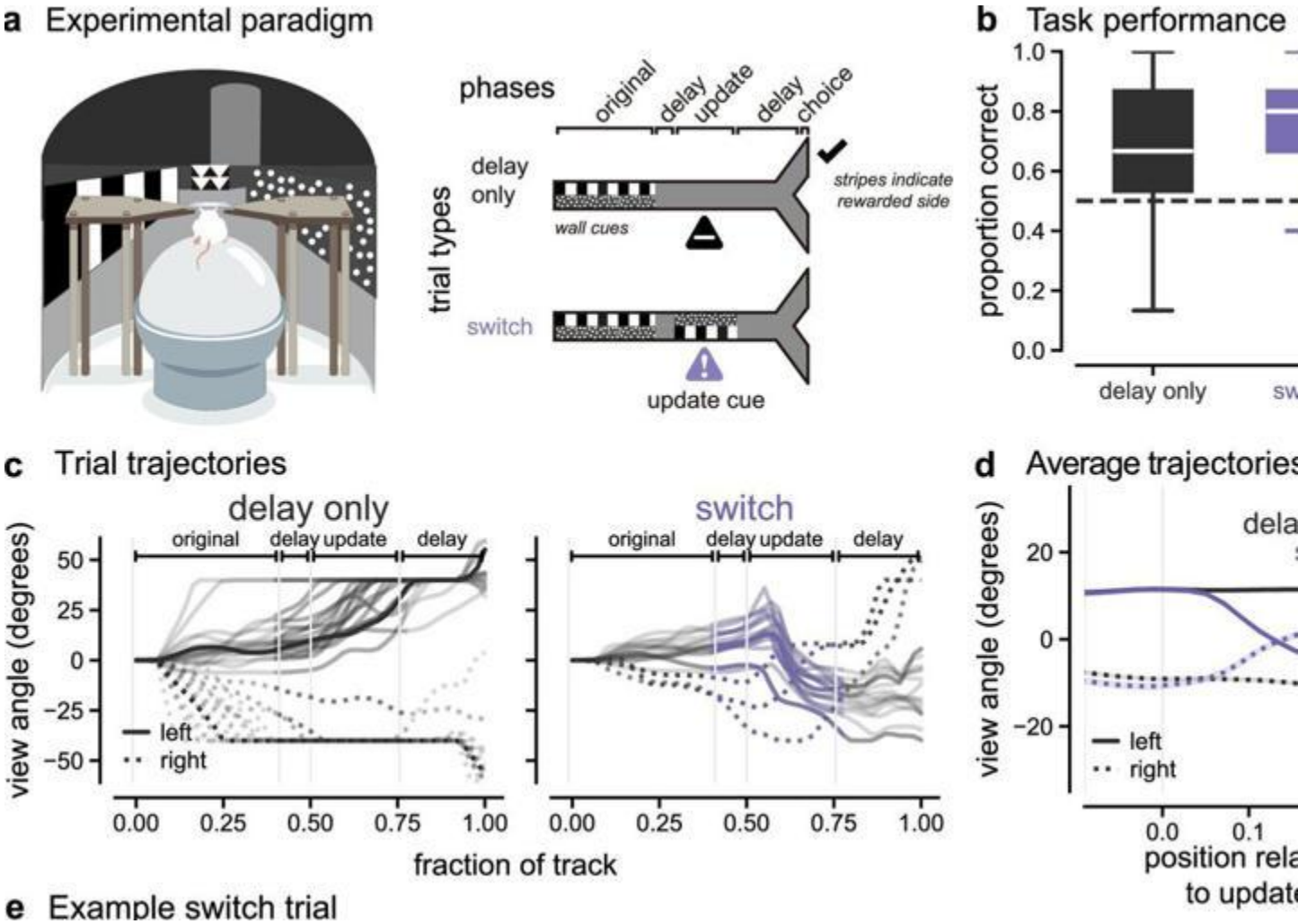
These insights not only shed light on the neural mechanisms of spatial navigation but also provide a foundation for exploring how the brain encodes information.

Prof. Burak explains, "The seemingly random firing patterns of place cells in large environments form 'codewords' that are uniquely assigned to different positions in space. We believe that the brain tunes the statistics of these random codewords to create a very efficient representation of positions in large environments".

More information: Nischal Mainali et al, Universal statistics of hippocampal place fields across species and dimensionalities, *Neuron* (2025). DOI: 10.1016/j.neuron.2025.01.017. www.cell.com/neuron/fulltext/S0896-6273(25)00043-1

Provided by Hebrew University of Jerusalem

How new information triggers the brain to navigate changing environments

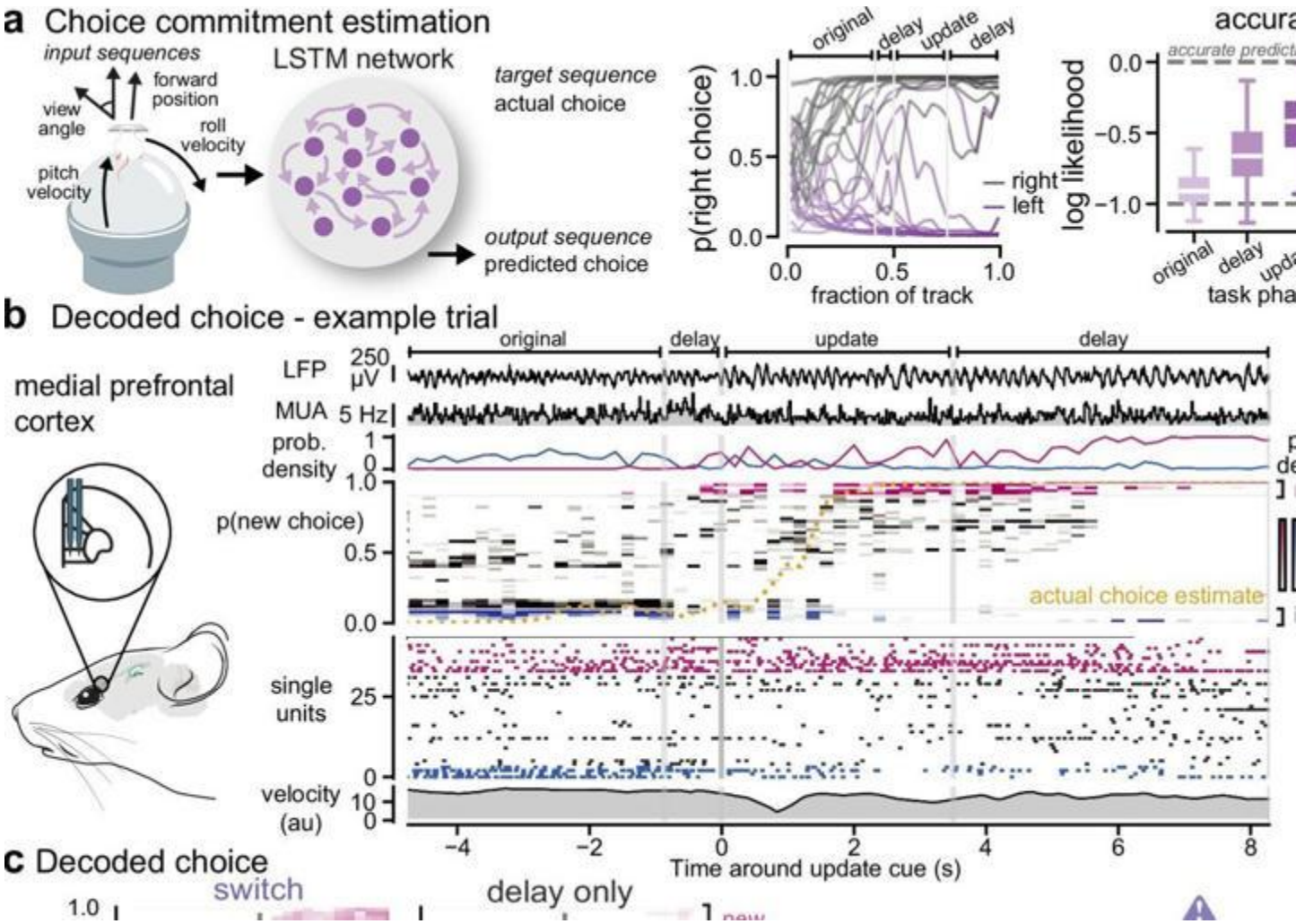


Mice rapidly and selectively update their choices in response to new information. Credit: Nature Communications (2025). DOI: 10.1038/s41467-025-60122-8

In a paper published in the journal *Nature Communications*, biomedical engineers have shown how two brain regions quickly adapt to shift focus from one planned destination to another.

Subscribe to our newsletter for the latest sci-tech news updates.

Stephanie Prince explains her research with a scenario many Atlantans can relate to. Imagine you're driving to the Atlanta airport to pick up a friend. They call to say they're in the terminal—but they're not sure which one. North, maybe? You head in that direction through the maze of roads around the airport.



Prefrontal cortex rapidly switches from representing the old to the new choice in response to new information. Credit: Nature Communications (2025). DOI: 10.1038/s41467-025-60122-8

Then they call back. They're actually in the South Terminal. So you make a quick mental adjustment and switch your route to arrive at the correct side of the airport.

You had a plan. You received new information. You quickly changed your destination.

The question Prince has studied is this: How does that process happen in the brain?

Her research is offering insights into that decision-making. And it could help scientists as they work to better understand when brain disorders such as Parkinson's and Alzheimer's impair those processes.

The study by Prince, Annabelle Singer, and other collaborators showed the new information prompted one brain region to quickly shift to representing both the original and new destinations simultaneously. Meanwhile, another region considering those choices rapidly switches to the new destination.

Researchers didn't know this dynamic change in brain activity takes place. Singer said it's important to learn because navigation planning is a good model for a variety of planning processes in the brain.

"Some of what we're looking at could apply to planning more broadly," said Singer, McCamish Foundation Associate Professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. "The other important aspect is that these systems go wrong in disease—including dementia and depression. Understanding the basic healthy processes is fundamental to then understanding how they go wrong in disease."

"We thought that maybe we would see some background information, but the two goal locations really dominate. That large increase of the brain representing both possible goals instead of one or the other was interesting."

Meanwhile, in the decision-making prefrontal cortex, the mouse's focus jumps from the initial destination to the new treat location, Prince said.

"That seems to happen before they've even changed their movement. It was really surprising to us to see those things happen so quickly."

To decipher how brains drive navigation in changing environments, Prince designed an experiment using a virtual reality maze that she could change on the fly. As mice navigated the simple maze in pursuit of a treat, Prince recorded data from thousands of neurons in two brain regions: the hippocampus and the prefrontal cortex.

Both showed significant activity changes.

"Most of the time, the animals have this GPS system in their hippocampus saying, 'this is where I am currently.' When we are presented new information, suddenly they're not thinking about where they are. Instead, they're thinking about the old goal and the new goal," said Prince, a former Ph.D. student in Singer's lab who now works as a scientific data engineer at Lawrence Berkeley National Lab.

The study helps address long-standing conflicting evidence in previous studies about what's actually being represented or encoded in the hippocampus and how activity there supports deliberation and planning.

More broadly, the findings offer new information about cognitive flexibility in the face of new information, Singer said.

She added, studying rodent navigation offers value because they're very good at it and that well-developed sense has parallels to what scientists have observed in humans.

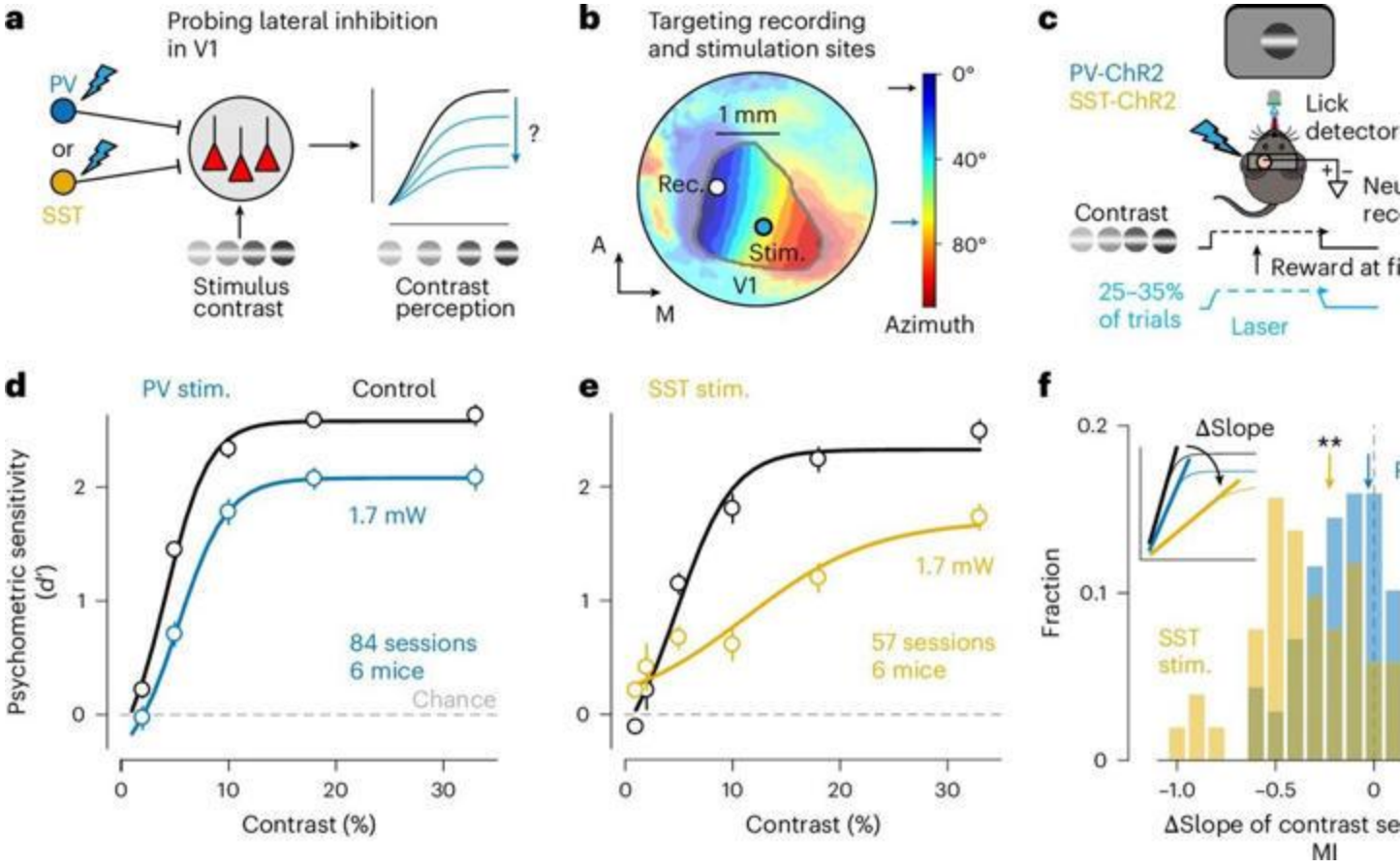
The lab isn't done with the detailed data Prince collected. Singer said the behavior they studied in these experiments is challenging. So her team is digging more into the large amount of neuron data to see what else they can discover.

More information: Stephanie M. Prince et al, New information triggers prospective codes to adapt for flexible navigation, *Nature Communications* (2025). DOI: 10.1038/s41467-025-60122-8

Provided by Georgia Institute of Technology

This story was originally published on Medical Xpress.

Sharper images: How the brain filters out the noise



SST lateral inhibition controls the slope of psychometric contrast sensitivity. Credit: Nature Neuroscience (2025). DOI: 10.1038/s41593-025-01888-4

A multidisciplinary team of researchers at Georgia Tech has discovered how lateral inhibition helps our brains process visual information, and it could expand our knowledge of sensory perception, leading to applications in neuro-medicine and artificial intelligence.

Lateral inhibition is when certain neurons suppress the activity of their neighboring neurons. Imagine an artist drawing, darkening the lines around the contours, highlighting the boundaries between objects and space, or objects and other objects. Comparably, in the visual system, lateral inhibition sharpens the contrast between different visual stimuli.

"This research is really getting at how our visual system not only highlights important things, but also actively suppresses irrelevant information in the background," said lead researcher Bilal Haider, associate professor in the Wallace H. Coulter Department of Biomedical Engineering. "That ability to filter out distractions is crucial."

Understanding how these inhibitory mechanisms work could provide insights into why people have trouble filtering out distractions or focusing on what's important in conditions like autism or ADHD.

"Our findings may also influence how we design artificial intelligence and neural networks," said Haider, whose team published its work this month in *Nature Neuroscience*. "Current AI systems treat all the computing units the same, but the brain has figured out how to assign specialized computing roles."

Joseph Del Rosario, a former graduate student in the Haider lab, was the lead author. Another key contributor was Hannah Choi, assistant professor in the School of Mathematics, and her Research Group in Mathematical Neuroscience. Their team built computational models to test the biological findings.

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"Collaborating with mathematicians to really understand the computational principles underlying these inhibitory processes is a great example of how neuroscience can inform fields like AI," Haider said.

Fine-tuning perception

The study focused on two types of inhibitory neurons in the visual cortex: parvalbumin (PV) neurons and somatostatin (SST) neurons. The researchers used

optogenetics—a technique that uses light to control cell activity—to activate PV and SST neurons in the visual cortex of mice. What they observed was striking.

"What's fascinating is that different types of inhibitory neurons seem to be doing distinct mathematical computations to achieve this suppression of the visual field," Haider said. "It's not a one-size-fits-all process."

When the team activated PV neurons, visual contrast sensitivity was evenly reduced, like lowering the brightness on a computer monitor. Activation of SST neurons resulted in a more nuanced change, altering the slope of the contrast sensitivity curve, which is a graph showing how well your visual system can detect contrast.

"Basically, SST neurons fine-tune our perception of contrast more strongly by reducing extra, unnecessary signals," Haider said. "That's lateral inhibition at work. These inhibitory neurons play a major role in our perception. The brain has evolved this precise wiring and division of labor among different neuron types to act as the brakes in the visual system, just as important as the accelerator."

The impact of lateral inhibition goes beyond the visual system. Similar processes may also be at work in other senses, like hearing and touch. As scientists develop a better understanding of how the brain filters sensory information, they may discover new ways to enhance or restore our overall sensory experience.

Haider first conceived the idea for this work 10 years ago when he was a postdoc. He believes the research could possibly result in new treatments for visual disorders, and lead to more flexible AI.

More information: Joseph Del Rosario et al, Lateral inhibition in V1 controls neural and perceptual contrast sensitivity, *Nature Neuroscience* (2025). DOI: 10.1038/s41593-025-01888-4

Provided by Georgia Institute of Technology

JULY 7, 2025

The GIST

Steering brain cells with magnetic nanoparticles to rebuild lost connections

by Kyoto University edited by Lisa Lock, reviewed by Robert Egan

Nano-pulling of NES cells transplanted in the VM/ST. Credit: *Advanced Science* (2025). DOI: 10.1002/advs.202500400
A collaborative study led by Professor Vittoria Raffa at the University of Pisa and Assistant Professor Fabian Raudzus (Department of Clinical Application) has unveiled a novel approach that uses magnetically guided mechanical forces to direct axonal growth, aiming to enhance the effectiveness of stem cell-based therapies for Parkinson's disease (PD) and other neurological conditions.

Parkinson's disease is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra (SN), which project to the striatum (ST) via the nigrostriatal pathway. The loss of these connections leads to dopamine deficiency and the onset of motor symptoms.

While cell replacement therapies using human stem cell-derived dopaminergic progenitors have shown encouraging results in clinical trials, a key limitation remains: the inability to guide the axons of transplanted cells over long distances to their appropriate targets in the adult brain.

To address this, the researchers developed a technique—called nano-pulling—to leverage magnetic nanoparticles (MNPs) and external magnetic fields to apply controlled mechanical forces within transplanted neural cells, thereby guiding their axonal extensions to target brain regions.

To test this system, the research team first constructed an organotypic brain slice model that mimics early-stage PD by co-culturing brain sections containing SN and ST. They transplanted human neuroepithelial stem (NES) cells, preloaded with MNPs, into the SN region. Upon exposure to a magnetic field, the MNPs generated piconewton-scale forces within the cells, stimulating axonal growth in the direction of the magnetic gradient.

The study, now published in *Advanced Science*, found that nano-pulling significantly enhanced the length and alignment of neural projections toward the striatum. Transplanted cells exhibited increased branching, greater synaptic vesicle formation, and improved microtubule stability—key indicators of neuronal maturation and functional integration.

These effects were observed in both NES cells and human iPS cell-derived dopaminergic progenitors, thus demonstrating the versatility and clinical relevance of the approach.

Importantly, the use of magnetic nanoparticles and magnetic fields—both of which are already employed in clinical imaging and therapeutic applications—supports the translational potential of nano-pulling. The researchers also confirmed that the technique did not compromise cell viability or tissue integrity, even after extended periods of mechanical stimulation.

This work represents a significant step forward in the development of regenerative therapies for neurodegenerative diseases. By enabling the reconstruction of the nigrostriatal pathway through guided axon growth, nano-pulling could enhance the efficacy of cell transplantation strategies and help restore functional connectivity in the brain.

Future studies will focus on optimizing nanoparticle properties, evaluating long-term outcomes in vivo, and exploring the broader applicability of this technique in other models of central nervous system injury and disease.

More information: Sara De Vincentiis et al, Mechanical Forces Guide Axon Growth through the Nigrostriatal Pathway in an Organotypic Model, *Advanced Science* (2025). DOI: 10.1002/advs.202500400
Journal information: Advanced Science
Provided by Kyoto University

JULY 9, 2025

Peripheral nerve regeneration driven by hundreds of unknown RNA molecules

by Weizmann Institute of Science edited by Gaby Clark, reviewed by Andrew Zinin

Top: Overexpression of genes from the B2-SINE family in retinal ganglion neurons led to accelerated growth after injury. Bottom: Ganglion cells after injury without B2-SINE overexpression. Credit: Weizmann Institute of Science
Unlike the brain and spinal cord, peripheral nerve cells, whose long extensions reach the skin and internal organs, are capable of regenerating after injury. This is why injuries to the central nervous system are considered irreversible, while damage to peripheral nerves can, in some cases, heal, even if it takes months or years. Despite decades of research, the mechanisms behind peripheral nerve regeneration remain only partially understood.

In a new study published in *Cell*, researchers from Prof. Michael (Mike) Fainzilber's lab at the Weizmann Institute of Science discovered that a family of hundreds of RNA molecules with no known physiological function is essential to nerve regeneration.

Remarkably, the study showed that these molecules can stimulate growth not only in the peripheral nervous system of mice but also in their central nervous system. These findings could pave the way for new treatments for a variety of nerve injuries and neurodegenerative diseases.

For a peripheral nerve to regenerate, it must maintain communication between the neuron's cell body and its long extension—the axon—which in humans can reach more than a meter in length. In a series of studies over the past two decades, Fainzilber's lab has revealed key components of this communication: proteins that act like postal couriers, delivering instructions for the production of growth-controlling factors and other proteins, from the cell body to the axon.

These molecular couriers also help assess the distance between the cell body and the axon tip, allowing the neuron to modulate its growth accordingly. Yet one central issue remained: What triggers the regenerative growth after injury, and why does this not happen in central nervous system cells?

In the new study, Dr. Indrek Koppel of Fainzilber's lab, in collaboration with Dr. Riki Kawaguchi of the University of California, Los Angeles (UCLA), examined a specific kind of gene expression in the peripheral nerves of mice following injury. The researchers were surprised to find that one day after damage, the neurons increased the expression of an entire family of short genetic sequences called B2-SINEs, whose role was previously unknown.

These sequences do not encode any proteins, and because they are known for "jumping" around the genome, meaning that they can appear at the wrong place or time, they have a bad reputation. But the researchers found that after injury, the neurons began expressing many B2-SINE RNA transcripts, in parallel with other processes preparing the cell for regeneration and repair.

Time-lapse of injured DRG axon growth under control conditions, related to Figure 2 Time-lapse imaging of regrowth of DRG neurons transduced with control AAV-Php.S after injury in spot cultures. Credit: *Cell* (2025). DOI: 10.1016/j.cell.2025.04.030
However, B2-SINE is an enormous family, comprising some 150,000 sequences scattered throughout the mouse genome. The initial analysis could not determine which of these were responsible for promoting growth.

Dr. Eitan Erez Zahavi, also of Fainzilber's lab, who led the new study alongside Koppel, used bioinformatics tools to identify 453 B2-SINE sequences that are highly expressed after injury, promoting nerve growth. Collaborating with international research teams, the scientists showed that this overexpression after injury is unique to peripheral nerve cells and does not occur in the central nervous system.

The periphery leads, the center follows

The researchers then tested whether B2-SINEs from peripheral nerve cells could also stimulate neuronal growth in the central nervous system. They induced retinal neurons in mice to overexpress RNA molecules of the B2-SINE type and observed faster regeneration after injury.

A similar experiment in the mouse motor cortex—the brain region that controls muscle movement via long axons projecting to the spinal cord—showed that neurons expressing high levels of B2-SINE also regenerated faster than control neurons.

"There are still no effective treatments to accelerate nerve cell growth and regeneration," Fainzilber notes. "While the growth acceleration observed in our study is not yet sufficient to address clinical paralysis, it is definitely significant. Of course, the path from basic research to clinical application is long, and we must make sure that enhancing growth mechanisms does not, for example, increase the risk of cancer."

Left: In motor cortex neurons of mice, overexpression of B2-SINE family genes led to accelerated cell regeneration after injury. Right: Injury in the same cells without B2-SINE overexpression. Credit: Weizmann Institute of Science
One final mystery remained: How do B2-SINE RNA molecules actually promote regeneration?

With help from Prof. Alma L. Burlingame's group at the University of California, San Francisco, the researchers discovered that these RNAs promote a physical link between the molecular "couriers" carrying instructions for producing growth-associated proteins and the ribosomes that read these instructions and carry them out. This means that production of the critical factors takes place closer to the cell body rather than to the tip of the axon. The researchers believe that this signals to the neuron that it is "too small," triggering a growth response.

"There are over a million sequences called Alu elements in the human genome, the human equivalent of B2-SINEs in mice," says Fainzilber. "These molecules had been previously shown to bind to ribosomes and mail couriers, but why this happens was unknown. We're now trying to determine whether Alu or other noncoding RNA elements are involved in nerve regeneration in humans."

"Recovery from peripheral nerve injuries, or from systemic diseases like diabetes that affect these nerves, can be very slow," he adds.

"That's why we're now testing a therapy that might speed up regeneration by mimicking B2-SINE activity. This therapy involves small molecules that connect the couriers to ribosomes while keeping them close to the nerve cell body, promoting faster growth. We are conducting this research in collaboration with Weizmann's Bina unit for early-stage research with applicative potential."

Beyond promoting peripheral nerve regeneration, the new study also hints at an even broader prospect: regeneration in the central nervous system. "We are currently working

with UCLA on a study showing that the mechanism we discovered plays a role in recovery from stroke in mouse models," Fainzilber says.

"Additionally, we're collaborating with Tel Aviv University, Hebrew University and Sheba Medical Center to study its possible role in ALS, a progressive neurodegenerative disease. Neurodegenerative conditions affect many millions of people worldwide. While the road ahead is long, I truly hope we'll one day be able to harness our newly discovered regeneration mechanism to treat them."

More information: Eitan Erez Zahavi et al, Repeat-element RNAs integrate a neuronal growth circuit, *Cell* (2025). DOI: 10.1016/j.cell.2025.04.030
Journal information: Cell
Provided by Weizmann Institute of Science

JULY 9, 2025

From injury to agony: Scientists discover brain pathway that turns pain into suffering

by Salk Institute edited by Stephanie Baum, reviewed by Andrew Zinin

CGRP-expressing neurons (green) in the parvocellular subparafascicular nucleus (SPFp) of the thalamus. Credit: Salk Institute
Pain isn't just a physical sensation—it also carries emotional weight. That distress, anguish, and anxiety can turn a fleeting injury into long-term suffering.

Researchers at the Salk Institute have now identified a brain circuit that gives physical pain its emotional tone, revealing a new potential target for treating chronic and affective pain conditions such as fibromyalgia, migraine, and post-traumatic stress disorder (PTSD).

Published in *Proceedings of the National Academy of Sciences*, the study identifies a group of neurons in a central brain area called the thalamus that appears to mediate the emotional (affective) side of pain in mice. This new pathway challenges the textbook understanding of how pain is processed in the brain and body.

"For decades, the prevailing view was that the brain processes sensory and emotional aspects of pain through separate pathways," says senior author Sung Han, associate professor and holder of the Pioneer Fund Developmental Chair at Salk. "But there's been debate about whether the sensory pain pathway might also contribute to the emotional side of pain. Our study provides strong evidence that a branch of the sensory pain pathway directly mediates the affective experience of pain."

The physical sensation of pain is what allows you to immediately detect it, assess its intensity, and identify its source. The affective part of pain is what makes it so unpleasant. This emotional discomfort motivates you to take action and helps you learn to associate negative feelings with the situation so you can avoid it in the future.

This is a critical distinction. Most people start to perceive pain at the same stimulus intensities, meaning we all process the sensory side of pain fairly similarly. In comparison, our ability to tolerate pain varies greatly. How much we suffer or feel threatened by pain is determined by our affective processing, and if it becomes too sensitive or lasts too long, it can result in a pain disorder. This makes it important to understand which parts of the brain control these different dimensions of pain.

Sensory pain was thought to be mediated by the spinothalamic tract, a pathway that sends pain signals from the spinal cord to the thalamus, which then relays them to sensory processing areas across the brain.

Affective pain had generally been thought to be mediated by a second pathway called the spinoparabrachial tract, which sends pain information from the spinal cord into the brainstem.

However, previous studies using older research methods have suggested the circuitry of pain may be more complex. This long-standing debate inspired Han and his team to revisit the question with modern research tools.

Using advanced techniques to manipulate the activity of specific brain cells, the researchers discovered a new spinothalamic pathway in mice. In this circuit, pain signals are sent from the spinal cord into a different part of the thalamus, which has connections to the amygdala, the brain's emotional processing center. This particular group of neurons in the thalamus can be identified by their expression of CGRP (calcitonin gene-related peptide), a neuropeptide originally discovered in Professor Ronald Evans's lab at Salk.

When the researchers "turned off" (genetically silenced) these CGRP neurons, the mice still reacted to mild pain stimuli, such as heat or pressure, indicating their sensory processing was intact. However, they didn't seem to associate lasting negative feelings with these situations, failing to show any learned fear or avoidance behaviors in future trials. On the other hand, when these same neurons were "turned on" (optogenetically activated), the mice showed clear signs of distress and learned to avoid that area, even when no pain stimuli had been used.

"Pain processing is not just about nerves detecting pain; it's about the brain deciding how much that pain matters," says first author Sukjae Kang, a senior research associate in Han's lab. "Understanding the biology behind these two distinct processes will help us find treatments for the kinds of pain that don't respond to traditional drugs."

Many chronic pain conditions—such as fibromyalgia and migraine—involve long, intense, unpleasant experiences of pain, often without a clear physical source or injury. Some

patients also report extreme sensitivity to ordinary stimuli like light, sound, or touch, which others would not perceive as painful.

Han says overactivation of the CGRP spinothalamic pathway may contribute to these conditions by making the brain misinterpret or overreact to sensory inputs. In fact, transcriptomic analysis of the CGRP neurons showed that they express many of the genes associated with migraine and other pain disorders.

Notably, several CGRP blockers are already being used to treat migraines. This study may help explain why these medications work and could inspire new nonaddictive treatments for affective pain disorders.

Han also sees potential relevance for psychiatric conditions that involve heightened threat perception, such as PTSD. Growing evidence from his lab suggests that the CGRP affective pain pathway acts as part of the brain's broader alarm system, detecting and responding to not only pain but a wide range of unpleasant sensations. Quieting this pathway with CGRP blockers could offer a new approach to easing fear, avoidance, and hypervigilance in trauma-related disorders.

Importantly, the relationship between the CGRP pathway and the psychological pain associated with social experiences like grief, loneliness, and heartbreak remains unclear and requires further study.

"Our discovery of the CGRP affective pain pathway gives us a molecular and circuit-level explanation for the difference between detecting physical pain and suffering from it," says Han. "We're excited to continue exploring this pathway and enabling future therapies that can reduce this suffering."

Other authors include Shijia Liua, Jong-Hyun Kima, Dong-Il Kima, Tae Gyu Oh, Jiahang Penga, Mao Yea, Kuo-Fen Lee, Ronald M. Evans, and Martyn Goulding of Salk.

More information: Sukjae J. Kang et al, Thalamic CGRP neurons define a spinothalamic pathway for affective pain, *Proceedings of the National Academy of Sciences* (2025). DOI: 10.1073/pnas.2505889122
Journal information: Proceedings of the National Academy of Sciences
Provided by Salk Institute

JULY 11, 2025

Graphene-based artificial tongue achieves near-human-like sense of taste

by Charles Blue, Phys.org edited by Sadie Harley, reviewed by Andrew Zinin

Schemes of the biological and graphene-oxide ionic sensory memristive device (GO-ISMD),-based gustatory systems. In the biological gustatory system, chemical stimuli first trigger the electrical responses through various taste receptor cells distributed on the tongue. These electrical potentials are subsequently encoded and transmitted via nerves to the cerebral cortical neurons for processing and taste recognition. In the GO- ISMD- based system, the sensing signals generated by feeding different saline flavors are first encoded and then imported to a dynamic GO- ISMD- based reservoir computing system for processing and perceiving. Credit: *Proceedings of the National Academy of Sciences* (2025). DOI: 10.1073/pnas.2413060122

A team of researchers report in the *Proceedings of the National Academy of Sciences* on a new graphene-based sensor design that, through machine learning, was able to develop a near-human sense of taste. This device is the first of its kind to operate in a moist environment, better approximating the conditions inside the human mouth.

The sensor described in the paper was made of multiple layers of graphene oxide, a material well known for its tunable electrical properties and high chemical reactivity, enclosed in a nanofluidic device.

Pure graphene—which was first isolated by Andre Geim and Kosta Novoslov, earning them the Nobel Prize in Physics in 2010—is a material made of a single layer of carbon atoms bound together in a lattice-like structure, endowing it with a range of mechanical, electrical, and chemical properties.

Like graphene, graphene oxide changes its electrical conductivity when exposed to different chemicals. The researchers used this property to measure electrical variations in the sensor when it was exposed to a sampling of 160 chemicals, each associated with a unique flavor profile. Using these data, a machine-learning algorithm was able to create a 'memory' of flavors.

This learning process is analogous to the way the human brain interprets signals from our taste buds when they react to chemicals in our foods. It was long held that humans could detect five distinct tastes: sweet, salty, bitter, sour, and umami. In 2023, researchers isolated a sixth flavor, ammonia chloride.

Schematic illustration of the device configuration. The size of the Graphene-oxide membrane is 4 mm × 4 mm. The scale bar in the SEM image is 500 nm.

Credit: *Proceedings of the National Academy of Sciences* (2025). DOI: 10.1073/pnas.2413060122
During testing, the new artificial tasting system's algorithm, which was trained to classify four basic tastes (sweet, salty, bitter, sour), could readily identify tastes it had already experienced with an accuracy of around 98.5%.

It was also able to categorize flavors of 40 samples it hadn't previously encountered, with an accuracy ranging from 75% to 90%. The researchers also trained the algorithm to identify the more complex tastes of coffee and cola.

Addressing one of the limitations of previous artificial gustatory systems (the technical term for similar artificial tongues), the new design integrated the sensing and computing functions of taste perception into a single nanofluidic device.

According to the authors, this system has the potential to one day restore taste perception to people who have lost that ability due to stroke, viral infection, or a range of neurodegenerative conditions. There are a number of technical hurdles to overcome before that time, however.

The complete system, which was designed as a proof-of-concept experiment, is relatively bulky with concurrently large energy demands. The researchers note that further miniaturization and integration are needed for practical applications.

Written for you by our author Charles Blue, edited by Sadie Harley, and fact-checked and reviewed by Andrew Zinin—this article is the result of careful human work. We rely on readers like you to keep independent science journalism alive. If this reporting matters to you, please consider a donation (especially monthly). You'll get an **ad-free** account as a thank-you.

More information: Yuchun Zhang et al, Confinement of ions within graphene oxide membranes enables neuromorphic artificial gustation, *Proceedings of the National Academy of Sciences* (2025). DOI: 10.1073/pnas.2413060122
Journal information: Proceedings of the National Academy of Sciences

JULY 11, 2025

Mathematical model reveals how humans store narrative memories using 'random trees'

by Ingrid Fadelli, Phys.org edited by Gaby Clark, reviewed by Robert Egan

Artistic image evoking the purpose of the study and created by Misha Tsodyks using LLMs. Credit: *Physical Review Letters* (2025). DOI: 10.1103/g1cz-wk1l

Humans can remember various types of information, including facts, dates, events and even intricate narratives. Understanding how meaningful stories are stored in people's memory has been a key objective of many cognitive psychology studies.

Researchers at the Institute for Advanced Study, Emory University and the Weizmann Institute of Science recently set out to model how humans represent meaningful narratives and store them in their memory, using mathematical objects known as "random trees." Their paper, published in *Physical Review Letters*, introduces a new framework for the study of human memory processes, which is rooted in mathematics, computer science and physics.

"Our study was aimed at solving a key challenge, namely creating a mathematical theory of human memory for meaningful material, such as narratives," Misha Tsodyks, senior author of the paper, told Medical Xpress. "The kind of consensus in the field is that narratives are too complex for such a theory to be possible, but I believe we proved this to be wrong—that despite the complexity, there are statistical trends in the way people recall narratives that can be predicted by a few simple basic principles."

To effectively model the representation of meaningful memories using random trees, Tsodyks and his colleagues used online platforms like Amazon and Prolific to perform recall experiments on a large number of subjects, using narratives borrowed from a paper by W. Labov. Essentially, they asked 100 people to recall 11 narratives of various lengths (ranging from 20 to 200 sentences) and later analyzed recorded recalls to test their theory.

"We chose a collection of spoken narratives recorded by a famous linguist W. Labov in the 1960s," explained Tsodyks. "We quickly realized that analyzing this amount of data requires modern AI tools in the form of recently developed large language models (LLMs).

"We then discovered that people don't simply recall various events from the narratives but often summarize relatively large parts of a narrative (such as episodes) in single sentences. This gave rise to an idea that a narrative is represented in memory as a tree where nodes that are closer to the root represent an abstract summary of larger episodes."

Tsodyks and his colleagues hypothesized that a tree representing a narrative is first constructed when an individual first hears or reads a story and understands it. As past studies suggest that individuals comprehend the same narratives differently, then the resulting trees would have unique structures.

"We formulated a model as an ensemble of random trees of a particular structure," said Tsodyks. "The beauty of this model is that it can be solved mathematically, and its predictions can be directly tested with the data, which we did. The main novelty of our random tree model of memory and recall is the assumption that any meaningful material is generically represented in the same fashion.

"Our study could have broader implications of this fact for human cognition because narratives seem to be a general way we reason about a wide range of phenomena in our individual lives and social and historical processes."

The recent work by this team of researchers highlights the promise of mathematical approaches and AI-based techniques for studying how humans store and represent meaningful information in their memories. In their next studies, Tsodyks and his colleagues plan to assess the extent to which their theory and random tree modeling approach could apply to other types of narratives, such as fiction stories.

"A more ambitious direction for future research will be to find more direct proofs for the tree model," added Tsodyks. "This would require designing other experimental protocols beyond simple recall. Brain imaging with people engaged in narrative comprehension and recall could be another interesting direction."

More information: Weishun Zhong et al, Random Tree Model of Meaningful Memory, *Physical Review Letters* (2025). DOI: 10.1103/g1cz-wk1l
Journal information: Physical Review Letters

JULY 11, 2025

Key brain protein may hold answers for memory loss and neurodegenerative diseases

by Rutgers University edited by Sadie Harley, reviewed by Andrew Zinin

Credit: Pixabay/CC0 Public Domain
Scientists have discovered how a key protein helps maintain strong connections between brain cells that are crucial for learning and memory.

Results of the study, published in the journal *Science Advances*, could point the way to new treatments for traumatic brain injuries and diseases, such as Parkinson's and Alzheimer's, the scientists said.

Their research, led by a Rutgers University-New Brunswick professor, uncovered a previously unknown role for cypin, a brain protein. Members of the research team found that cypin promotes the presence of tags on specific proteins at synapses, namely the tiny gaps where the brain cells, known as neurons, communicate. The marking helps ensure that the right proteins are in the right place, allowing the synapses to work properly.

The researchers said the insight has potentially profound implications for the treatment of brain disorders.

"Our research indicates that developing treatments or therapies that specifically focus on the protein cypin may help improve the connections between brain cells, enhancing memory and thinking abilities," said Bonnie Firestein, a Distinguished Professor in the Department of Cell Biology and Neuroscience in the School of Arts and Sciences and an author of the study.

"These findings suggest that cypin could be used to develop treatments for neurodegenerative and neurocognitive diseases, as well as brain injuries."

Firestein has been studying cypin for more than two decades. Her latest work uncovered several important aspects of how cypin functions and why it is significant for brain health.

One of the crucial discoveries is that cypin helps add a special tag to proteins in synapses connecting neurons. This tag ensures proteins are correctly positioned and able to send

signals effectively. Proper tagging and movement of proteins are essential for the neurons to function correctly.

Another important finding is that cypin interacts with a complex of proteins, known as the proteasome, which is responsible for breaking down proteins. When cypin attaches or binds to the proteasome, it slows down this breakdown process, leading to an accumulation of proteins. This buildup can positively affect various cellular functions, which are important for the communication between neurons.

Firestein's research also shows that when there is more cypin present, the levels of important proteins in the synapses increase. These proteins are vital for effective communication between neurons, empowering learning and memory.

Additionally, cypin increases the activity of another protein called UBE4A, which also helps with the tagging process. This indicates that cypin's influence on synaptic proteins is partly because of its effect on UBE4A.

The work highlights the importance of cypin in maintaining healthy brain function and its potential as a target for therapeutic interventions.

"Even though this study is what we call 'basic research," it can eventually be applied in practical, clinical settings," said Firestein, who is already conducting such "translational" work in parallel. Translational research is a type of research that takes discoveries made in the lab and turns them into practical treatments or solutions to improve human health.

Cypin's significant role in the workings of the brain's synapses makes it highly relevant to the potential treatment of neurodegenerative diseases and traumatic brain injury, she said. For example, healthy synaptic function is often disrupted in diseases such as Alzheimer's and Parkinson's.

In addition, the protein's role in promoting synaptic plasticity—the ability of synapses to strengthen or weaken over time—means it may be used to help counteract the synaptic dysfunction seen in neurodegenerative diseases and brain injuries.

Other scientists from Rutgers involved in the study include Kiran Madura, a professor in the Department of Pharmacology at Robert Wood Johnson Medical School; Srinivasa Gandu, Mihir Patel, and Ana Rodriguez, former doctoral students in the Department of Cell Biology and Neuroscience.

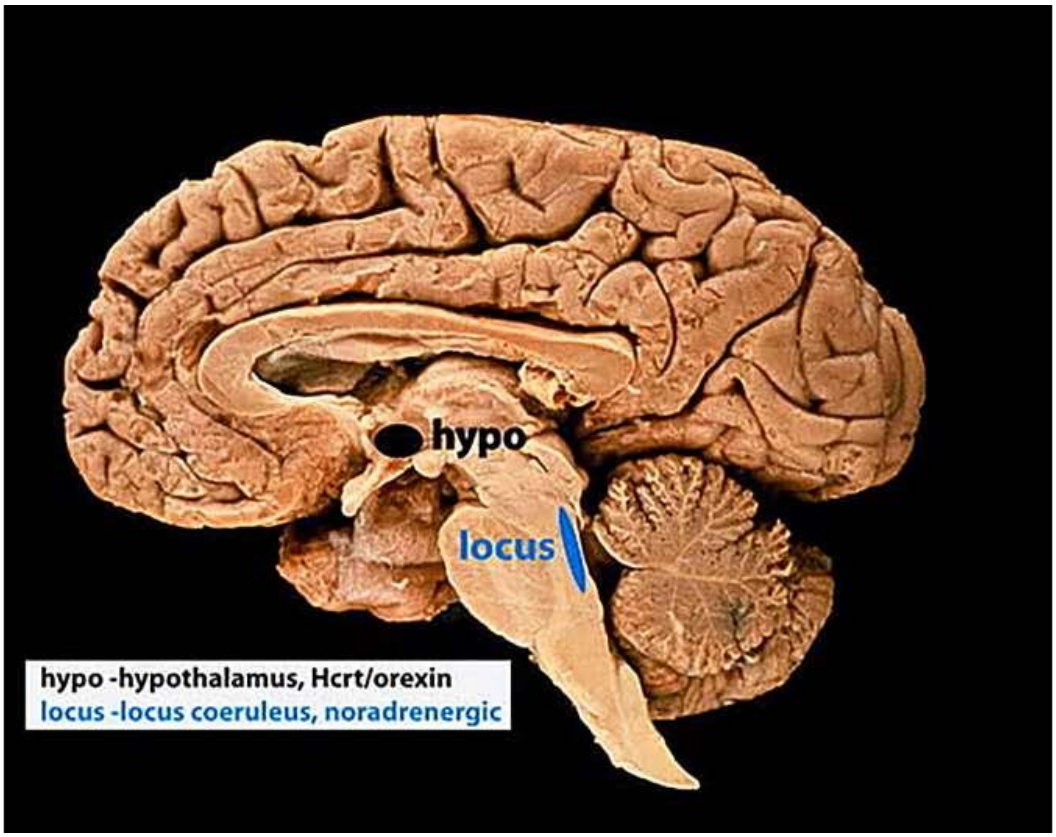
Jared Lamp and Irving Vega of Michigan State University also contributed to this research.

More information: Srinivasa Gandu et al, Cypin regulates K63-linked polyubiquitination to shape synaptic content, *Science Advances* (2025). DOI: 10.1126/sciadv.ads5467. www.science.org/doi/10.1126/sciadv.ads5467
Journal information: Science Advances
Provided by Rutgers University

JULY 15, 2025

AI-powered 'digital twin' created to predict personal health outcomes

by Weizmann Institute of Science edited by Gaby Clark, reviewed by Andrew Zinin



Variation of clinical and multi-omic data across ethnicities. Credit: *Nature Medicine* (2025). DOI: 10.1038/s41591-025-03790-9

Before an important meeting or when a big decision needs to be made, we often mentally run through various scenarios before settling on the best course of action. But when it comes to our health—be it choosing a treatment for an ailment or even selecting a dietary regimen—it is a lot harder to predict how each choice will affect our bodies and whether it will suit us personally.

Recently, researchers from Prof. Eran Segal's laboratory at the Weizmann Institute of Science have harnessed artificial intelligence to create a personalized "digital twin" that allows them to detect a risk of developing diseases, initiate preventive treatment and even run simulations to predict which treatment will be most effective. This new development, detailed in *Nature Medicine*, was made possible by the Human Phenotype

Project, in which scientists involved in the initiative, along with colleagues worldwide, have collected extensive, in-depth medical information from over 13,000 people.

Before the Human Genome Project was launched in 1990 to explore the fundamental question of what makes each of us who we are, only a fraction of human genes were known to science. The project led to the identification of tens of thousands of genes that shape our traits, and it revealed the genetic basis of numerous diseases.

Today, however, it is clear that genes alone provide only a partial picture. Many of the characteristics that define us and the diseases that threaten us are linked to environmental factors, the community of microorganisms residing in our bodies (our microbiome), the aging process and other factors.

In an effort to attain a broader picture, Segal, from Weizmann's Computer Science and Applied Mathematics Department, launched the Human Phenotype Project in 2018. This project tracks thousands of participants who undergo extensive medical assessments and testing every two years over a 25-year period. These evaluations cover 17 different body systems and include a wide array of tests, such as body measurements, nutritional logs, ultrasounds, bone mineral density tests, voice recordings, home sleep tests, continuous glucose monitoring over two-week periods, gene sequencing, cellular protein analysis and microbiome analysis of samples from the gut, vagina and oral cavity.

"When we launched the project in Israel in 2018, our initial goal was 10,000 participants," Segal says. "Since then, more than 30,000 people have signed up, and we hope to reach 100,000 in the future. To deepen our understanding of ethnic, environmental and cultural variations, we set up a branch in Japan and are currently finalizing the establishment of another in the United Arab Emirates, in collaboration with Professor Eric Xing from the Mohamed bin Zayed University of Artificial Intelligence.

"We are also broadening the age range of our participants. Initially, we recruited people between 40 and 70 years of age, but now younger and older people are also joining the study. This research has led to the creation of an advanced database that is not only extensive but also represents the most in-depth collection of human data currently in existence.

"We recognized the importance of sharing this resource with the scientific community and have now made it accessible digitally to research groups worldwide, while maintaining the privacy of the participants. We believe that the data we have compiled will profoundly affect the field of medicine."

What's your biological age?

Modern medicine largely relies on conducting tests and comparing the results to the average ranges for a person's age and sex. However, the underlying health status and the aging process vary considerably among individuals.

A research team led by Drs. Lee Reicher and Smadar Shilo from Segal's lab has developed an AI model that studies typical physiological changes, which occur throughout a person's lifespan, in 17 human body systems and learns to identify deviations from expected patterns. The model is built on a platform developed by Pheno.AI, a company specializing in AI research for health care.

"The model assigns scores to each body system and compares these values to the expected values for the participant's chronological age, sex and body mass index," explains Segal. "Based on the deviation from these predicted values, the model determines the participant's biological age. The older the apparent age of a body system, the greater the risk of associated diseases.

"For instance, by tracking participants' glucose levels, we determined the normative rate of increase in blood sugar for men and women over the years. Our model detects any deviation from this pattern and thus successfully identifies pre-diabetes in 40% of people who were classified as healthy by conventional testing methods."

The study of biological age has revealed significant differences between the sexes. "While men's biological age generally increases relatively linearly, we observe an acceleration in women's biological aging during their fifth decade of life," Segal notes.

"Menopause is a pivotal event in many medical respects, and it appears to reset the biological age clock. For example, we found that a decrease in bone density is more strongly correlated with the time that passed since the onset of menopause than with chronological age. Furthermore, our measurements make it possible to detect the start of menopause early, so that hormonal treatment can be planned accordingly."

The Human Phenotype Project has also uncovered new avenues for the early diagnosis of a multitude of medical conditions, including breast cancer, inflammatory bowel disease and endometriosis. That's because these conditions are characterized by a change in the composition of the patient's microbiome, and this change acts as a unique and identifiable "signature."

Still, the most significant promise of the Human Phenotype Project lies in its potential to advance personalized or precision medicine. Researchers aim to achieve this through a unified computer model that will integrate all the information collected from each participant in the project, creating a digital twin of that person. This model—currently under development, in a project led by doctoral student Guy Lutsker—will predict what medical events the participant is likely to experience in the future and how best to prevent them.

To train the model, the scientists let it study the medical records of each participant and then ask it to make minor predictions. A specific piece of information is withheld each time, and the model is tasked with predicting it based on the existing data. This training approach helps create a generative AI model that can predict medical events and in the future is expected to construct an entire personalized "health trajectory" outlining a person's future health status years in advance.

The research team has already developed a model that, by analyzing participants' glucose levels, has successfully predicted not only their future glucose levels but also which pre-diabetic individuals are at the highest risk of developing diabetes within the next two years. Such predictions help prevent the disease, or delay it at an early stage. Moreover, the researchers are already using the digital twin to check which dietary changes or drugs would be most beneficial for each participant.

In the future, the model is expected to encompass all the information within the database, enabling it to predict a wide range of medical events and spare patients the often lengthy trial-and-error process of finding the most effective treatment.

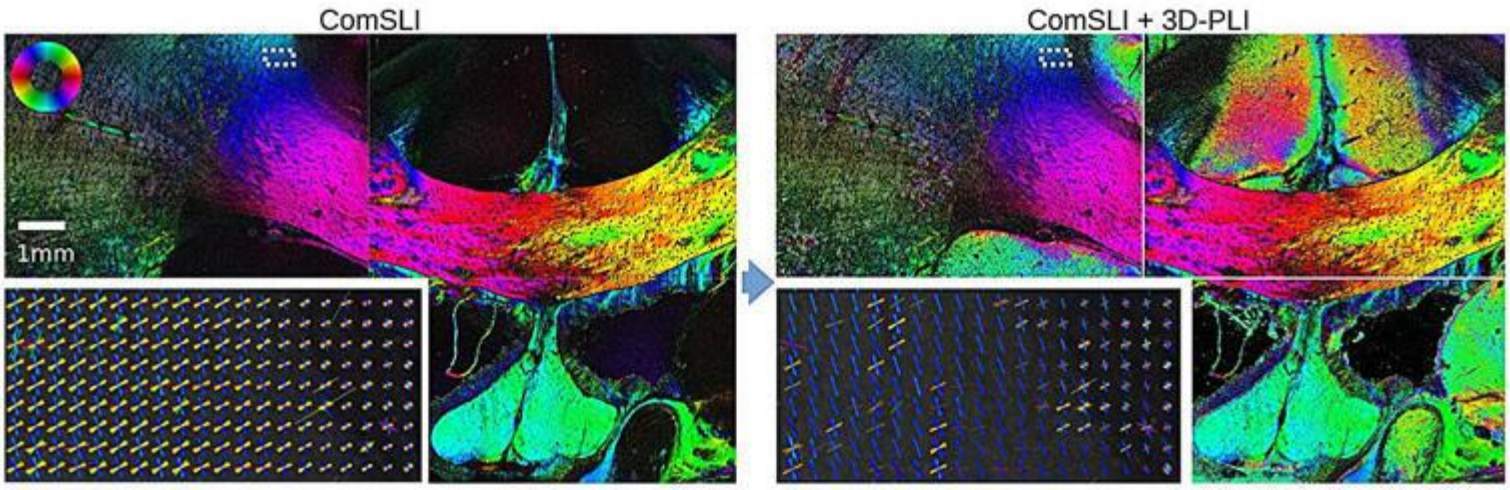
"This achievement is primarily made possible by the community of participants in the Human Phenotype Project. It is a dedicated group of individuals committed to advancing medicine and to the continuous monitoring of their health. We are developing an application that will bring all the collected information to the participants' fingertips and in the future will provide them with a personal 'health trajectory,'" Segal adds.

"We are living in an era of incredibly rapid change. The realms of health and medicine will undergo dramatic transformations in the coming years, becoming increasingly AI-driven.

"Our project is poised to be a leading global source of information and innovation, and this is all thanks to our participants. I want to take this opportunity to express my sincere gratitude to each and every one of you—your exceptional collaboration is the true driving force behind this revolution in medicine."

More information: Lee Reicher et al, Deep phenotyping of health–disease continuum in the Human Phenotype Project, *Nature Medicine* (2025). DOI: 10.1038/s41591-025-03790-9
Journal information: Nature Medicine
Provided by Weizmann Institute of Science

New instrument for enhanced imaging of nerve fibers in the brain



Nerve fiber pathways Nerve fiber tracts in three brain regions, color-coded. The scattering polarimeter combines the measured fiber directions of ComSLI and 3D-PLI (right), resulting in a better signal than with ComSLI alone (left). The improvement is particularly noticeable in regions with few nerve fibers and leads to fewer erroneous directions (vector maps bottom left). Credit: Scientific Reports (2025). DOI: 10.1038/s41598-025-02762-w

In order to understand the structure and functioning of the brain, neuroscientists need to study the complex, three-dimensional pathways and connections of nerve fibers. The intersection of multiple nerve fibers poses a particular challenge for neuroimaging.

Until now, two methods—3D-PLI and ComSLI—have been used separately. Researchers from Jülich and Delft have developed a system that combines both methods to great advantage. They present their "Scattering Polarimeter" in a recent study published in the journal *Scientific Reports*.

Advantages of the combination

3D Polarized Light Imaging (3D-PLI) makes it possible to visualize the course of nerve fibers in entire histological brain sections with a resolution in the

micrometer range using visible light. However, the method leaves uncertainties in pixels that contain intersecting nerve fibers. This problem can be solved with the help of Computational Scattered Light Imaging (ComSLI): The same brain slices are illuminated (now automated) from different angles and the transmitted (scattered) light is measured under normal incidence.

This produces light intensity profiles that reveal the underlying brain tissue structure and thus the crossing of nerve fibers. A combination of both methods in a single device would offer decisive advantages: faster measurements, pixel-by-pixel mapping and cross-validation of fiber courses.

The Scattering Polarimeter, potential applications and JUPITER

To this end, the researchers developed the "Scattering Polarimeter" based on the so-called Mueller polarimeter: a microscope that enables simultaneous 3D-PLI and ComSLI measurements during large-scale brain scans.

Initial studies of brain slices from different species using the Scattering Polarimeter have already shown results comparable in quality to the individual measurements of 3D-PLI and ComSLI, and can be used for high-precision multimodal maps of nerve fiber tracts. Scientists now see good opportunities for the micrometer-precise reconstruction of neural networks of the human brain. The capacities of the new Jülich exascale computer JUPITER will also be used for this purpose.

More information: Franca auf der Heiden et al, Scattering polarimetry enables correlative nerve fiber imaging and multimodal analysis, *Scientific Reports* (2025). DOI: 10.1038/s41598-025-02762-w

Provided by Jülich Research Center

Scientists reveal a widespread but previously unidentified psychological phenomenon

Many people will continue with a longer, less efficient path to a goal rather than backtrack and take a shortcut — even when the backtracking would save time and effort. A new series of studies published in *Psychological Science* reveals that this behavior, called "doubling-back aversion," emerges in both physical and mental tasks, and is driven not by mistaken cost estimates but by how people think about their past and future effort.

Psychologists have long studied why people stick with inefficient paths. The status quo bias describes the tendency to prefer current arrangements, while the sunk-cost fallacy highlights how people keep investing in failing efforts to justify past choices. But these don't quite explain situations where people are choosing among equally new options — except that one feels like it erases what's already been done.

Two researchers at UC Berkeley — Kristine Y. Cho, a PhD student, and Clayton R. Critcher, the Joe Shoong Professor of Business — sought to investigate whether people really do avoid doubling back, even when it's objectively better, and to identify why.

"We both had a strong intuition that we kept circling back to as we developed our research," Cho explained. "The idea was this: Imagine you're walking from your house to a friend's place. You leave your front door, turn left, and head down the block. But then you realize that you would get there faster if you had gone right instead."

"At this point, you're still close enough to home that retracing your steps, passing your front door, and taking the better route would actually save time. But would most people actually turn around and walk past where they started? We didn't think so. That reluctance to reverse course, even when it's clearly better, seemed to pop up a lot in real life. So we set out to investigate it."

Across four experiments involving more than 2,500 adults from the United States, researchers tested whether people avoided more efficient strategies if they involved retracing their steps or restarting a task. The studies used both virtual navigation and cognitive tasks to examine the phenomenon in different contexts.

In the first study, college students used a virtual reality interface to move from one location to another. After walking a short distance, they encountered a map offering two paths to the destination. One path was shorter but required them to double back — literally reversing the steps they had just taken. Even though the shorter route would get them there faster, many avoided it when it required backtracking.

Subsequent studies replaced physical movement with mental effort. In one task, participants had to generate 40 words starting with the letter "G." After listing 10, they were given a choice: continue with "G" words or switch to "T" words — a task expected to be easier. The tasks were objectively equivalent except for one difference: in one version, the new task was described as "starting over" and discarding previous work, while in the other version, it was described as "continuing the task under new instructions." Both versions involved writing 30 more words, but only the "start over" version framed the switch as undoing progress.

In a third experiment, the researchers split doubling back into two components: deleting past work and having to complete the entire task from the beginning again. They manipulated how each component was framed and assessed how participants responded. The final study added a more detailed set of questions to examine how participants viewed their past and future efforts depending on their decision to switch tasks or stay the course.

Across all four studies, people consistently avoided options that involved doubling back, even when those options saved time. In the virtual reality study, only 31% of participants chose the shorter path when it required retracing their steps, compared to nearly 57% when it did not. In the word-generation tasks, framing the switch as "starting over" reduced the likelihood of switching from 75% to just 25%.

"The sheer size of the effect caught us off guard," Cho told PsyPost. "For instance, take Study 2 in our paper. In that study, we told participants that they would have to list 40 words starting with the letter 'G.' But after they listed 10 words starting

with ‘G’, we gave them the option to switch to listing words starting with the letter ‘T’. Because more words in the English language start with ‘T’ than ‘G’, switching essentially made the task easier. And when the choice was framed simply as a choice to switch letters for the remainder of the task, 75% of participants did indeed choose to switch to the easier task.”

“But when the choice was framed as ‘doubling back,’ that is, discarding their progress and starting over on a new task with 30 new ‘T’ words, only 25% switched. The contrast was so stark that my first reaction was to suspect a coding error, that maybe we had accidentally reversed the responses. But after carefully checking the data multiple times, we confirmed it was correct. The effect wasn’t just real, it was strikingly strong.”

Importantly, this aversion was not explained by a belief that the backtracking route would take longer. Participants generally understood that switching would save time. But they still chose to stay the course when switching was described as discarding previous work or restarting the task.

The researchers found that doubling-back aversion was driven by how people mentally interpreted their efforts. When switching tasks was framed as undoing work, participants felt that their earlier effort had been wasted. This made the remaining work feel less like a path to success and more like an uphill slog. The effect was stronger when participants believed they had to start from scratch rather than continue with a portion of the work.

The aversion was strongest when both components of doubling back were present — undoing past work and starting over with a full task. But each factor independently contributed to the effect. In other words, people were less likely to switch to a faster strategy even if only one part of doubling back was invoked.

The researchers also tested whether participants’ decisions were shaped by how much time they thought each path would take. Although people generally did think switching would be quicker, these perceptions didn’t fully explain their choices. Instead, people were more influenced by subjective impressions about what switching meant for their progress and future effort.

“Our research shows that people often avoid backtracking, even when changing course would clearly get them to their goal faster,” Cho explained. “This hesitation stems from a discomfort with ‘wasting’ past effort, but in reality,

refusing to double back often leads to even more wasted time and energy. Our key takeaway is this: Progress isn't always about pushing forward. Sometimes, the smartest move is to step back, reassess, and choose the better path, even if it means undoing what's already been done."

While the experiments captured doubling-back aversion in controlled settings, real-life decisions are often messier. Future research might explore how this bias plays out in more complex or emotionally charged scenarios — such as changing careers, relationships, or long-term projects.

"We examined doubling back aversion in the context of tasks that take just a few minutes to complete," Cho noted. "But we expect that if anything, for more complex and longer tasks, doubling back aversion might be even stronger as people might become even more averse to viewing their longer past efforts as a waste."

The studies also did not test ways to reduce doubling-back aversion. However, the researchers suggested that encouraging people to focus on future gains rather than past losses could help. For example, reframing a switch as a time-saving opportunity rather than a "restart" may reduce resistance.

This focus on how people mentally frame past effort and future potential has also shaped the researchers' broader work. As Cho explained: "In our work on doubling-back aversion, we explored how people resist switching tactics midway, even when doing so would help them reach their goals more efficiently. More recently, we've been examining a related form of hesitation. This time, it's not in switching paths, but in committing to one at all."

"While it might seem that having enticing options (e.g., a great apartment one could rent, a fun event one could sign up for) would make commitment easier, we've found that it's often the loss of a great option that finally pushes people to choose. People often hold out for something even better, but the disappearance of a pretty good option inspires some pessimism that encourages people to grab onto what is as good as they can get for now."

"A theme that this suggests is that people are too past focused, worrying about feeling that they have made good use of their time and efforts," Cho added. "But people need to recognize that the past is fixed, and it is only the future we can control. We need to be willing to accept that we may have made some mistakes

along the way, but that is never too late to change course, especially when doing so will get us to where we want to go more quickly."

The study, "Doubling-Back Aversion: A Reluctance to Make Progress by Undoing It," was published May 9, 2025.

JULY 18, 2025

Why do we need sleep? Researchers find the answer may lie in mitochondria

by University of Oxford edited by Lisa Lock, reviewed by Andrew Zinin

Sleep may not just be rest for the mind—it may be essential maintenance for the body's power supply. A new study by University of Oxford researchers, published in *Nature*, reveals that the pressure to sleep arises from a build-up of electrical stress in the tiny energy generators inside brain cells.

The discovery offers a physical explanation for the biological drive to sleep and could reshape how scientists think about sleep, aging, and neurological disease.

Led by Professor Gero Miesenböck from the Department of Physiology, Anatomy and Genetics (DPAG), and Dr. Raffaele Sarnataro at Oxford's Center for Neural Circuits and Behavior, the team found that sleep is triggered by the brain's response to a subtle form of energy imbalance. The key lies in mitochondria—microscopic structures inside cells that use oxygen to convert food into energy.

When the mitochondria of certain sleep-regulating brain cells (studied in fruit flies) become overcharged, they start to leak electrons, producing potentially damaging byproducts known as reactive oxygen species. This leak appears to act as a warning signal that pushes the brain into sleep, restoring equilibrium before damage spreads more widely.

"You don't want your mitochondria to leak too many electrons," said Dr. Sarnataro. "When they do, they generate reactive molecules that damage cells."

The researchers found that specialized neurons act like circuit breakers—measuring this mitochondrial electron leak and triggering sleep when a threshold is crossed. By manipulating the energy handling in these cells—either increasing or decreasing electron flow—the scientists could directly control how much the flies slept.

Even replacing electrons with energy from light (using proteins borrowed from microorganisms) had the same effect: more energy, more leak, more sleep.

Professor Miesenböck said, "We set out to understand what sleep is for, and why we feel the need to sleep at all. Despite decades of research, no one had identified a clear physical trigger. Our findings show that the answer may lie in the very process that fuels our bodies: aerobic metabolism.

"In certain sleep-regulating neurons, we discovered that mitochondria—the cell's energy producers—leak electrons when there is an oversupply. When the leak becomes too large, these cells act like circuit breakers, tripping the system into sleep to prevent overload."

The findings help explain well-known links between metabolism, sleep, and lifespan. Smaller animals, which consume more oxygen per gram of body weight, tend to sleep more and live shorter lives. Humans with mitochondrial diseases often experience debilitating fatigue even without exertion, now potentially explained by the same mechanism.

"This research answers one of biology's big mysteries," said Dr. Sarnataro. "Why do we need sleep? The answer appears to be written into the very way our cells convert oxygen into energy."

More information: Raffaele Sarnataro et al, Mitochondrial origins of the pressure to sleep, *Nature* (2025). DOI: 10.1038/s41586-025-09261-y
Journal information: Nature

JULY 15, 2025

Scientists unravel how a tiny region of the brain helps us form distinct memories

by Holly Ober, University of California, Los Angeles edited by Gaby Clark, reviewed by Andrew Zinin

Life may unfold as a continuous stream, but our memories tell a different story. We do not recall the past as one long, unbroken text. Instead, we remember it as a series of meaningful events, like how sentences are structured with grammar and punctuation. Like any narrative, this organization gives our experiences shape and coherence, helping us make sense of what and when things happen.

The brain must devote a lot of space to this herculean task, right?

Wrong! It turns out that a tiny but mighty region pulls far more than its weight.

In a paper published in the journal *Neuron*,locus coeruleus, acts like a "memory reset button" during meaningful changes.

"Our key question was: as an experience unfolds, how does the brain 'know' when one meaningful memory has ended and the next should begin?" said UCLA psychology

professor and first author David Clewett. "Research has shown that remaining in a stable context, such as the same room, binds sequential experiences together in memory.

"By contrast, experiencing a shift in context, or event boundary, drives memories apart to represent distinct events. In this way, context acts as the grammar of human memory. What we found is that the locus coeruleus is most active at event boundaries when memories become separated. Thus, this small region at the core of the brain's arousal system may serve to punctuate our thoughts and memories."

Clewett and co-authors Ringo Huang at UCLA and Lila Davachi at Columbia recruited 32 volunteers who looked at pictures of neutral objects while inside an MRI scanner. To manipulate whether the surrounding context was stable or changing, simple tones were played in either the right or left ear.

Eight pure tones were repeated in the same ear to create a sense of a coherent event, then the tone switched to the other ear and changed in pitch to elicit perception of an event boundary. This repeat-switch pattern continued throughout the remainder of the sequence, creating the perception of four different auditory events.

The researchers then tested how these tone switches influenced memory. They reasoned that time provides a window into how events are formed: when people successfully reconstruct the order of a sequence, it suggests these items are linked within a single memory. In contrast, it is harder to remember the precise sequence of events when they have been stored in separate, distinct memories.

As they predicted, locus coeruleus activation at event boundaries predicted later memory separation, as shown by worse ability to remember the order of item pairs that spanned boundaries. The researchers also cross-checked their measurements of locus coeruleus activation against eye pupil dilation measurements taken at the same time, because pupils are known to dilate slightly both as new events occur and when the locus coeruleus is active.

These measurements confirmed that observations during the fMRI were indeed capturing activation in this small brain area. Functional magnetic resonance imaging, or fMRI, measures brain activity by detecting changes in blood flow while a person is inside the scanner.

The consequences of this neural and memory reset signal were far-reaching. Stronger locus coeruleus activation at boundaries between events predicted larger changes in activation patterns within the hippocampus, a brain region that tracks contextual details like place and time and is central to the formation of new memories.

"Part of the job of the hippocampus is to map the structure of our experiences, so it has an index of the beginning, middle and ends of events. We found that the locus coeruleus may provide the critical 'start' signal to the hippocampus, as if saying, 'Hey, we're in a new event now,'" said Davachi.

"Prior work had shown that bursts of locus coeruleus activity help reconfigure brain networks to direct attention to new and important experiences. Our findings suggest that this updating signal is even more widespread, also reaching memory-related regions that carry representations of ongoing events."

The researchers also examined how brief bursts of locus coeruleus activation are influenced by background levels of locus coeruleus activity. This matters because locus coeruleus neurons operate in two distinct modes: a burst-like mode that flags significant events and forms new memories, and a background mode that regulates general alertness and stress.

"The locus coeruleus is like the brain's internal alarm system," Clewett said. "But under chronic stress, this system becomes overactive. The result is like living with a fire alarm that never stops ringing, making it difficult to notice when a real fire breaks out."

Although the dynamic interplay between these firing patterns has been studied in the context of decision-making, perception and learning, its relevance for how we perceive and remember events has, thus far, been unclear.

So, the authors set out to test whether bursts of locus coeruleus activation at event boundaries, the neural signals that segment memories, might be weakened or lost under conditions of chronic stress. This question posed a challenge, as fMRI alone cannot measure absolute levels of stress or locus coeruleus activation. To address this, they used an imaging method that indirectly measures neuromelanin, a pigmented neurochemical that accumulates in the locus coeruleus with repeated activation over time.

As predicted, participants with a higher neuromelanin-related signal, thought to indicate chronic stress, showed weaker pupil dilation responses to event boundaries. Stronger low-frequency fluctuations in locus coeruleus activation, a proxy for background levels of activity, also predicted weaker spikes in locus coeruleus activation and pupil responses to boundaries during the task. Together, these findings suggest that chronic hyperarousal may blunt one's sensitivity to change, disrupting the cues that anchor and organize new episodes in memory.

Identification of the locus coeruleus as the gateway or conductor for memory formation may lead to better ways to treat PTSD and other memory-related disorders, such as Alzheimer's disease, where the locus coeruleus is unusually hyperactive. There are potential ways to quiet an overactive locus coeruleus, whether pharmacologically or through slow-paced breathing or even hand-squeezed stress balls.

But good long-term solutions require further research and will take time to discover and bring to market. Perceiving events in the "right" way is directly linked to better memory, suggesting that improving locus coeruleus function is an effective target for either protecting or recovering memory function.

"Conducting basic science and clinical research is critical for opening new doors for treating debilitating disorders," Clewett said. "Recent legislative actions threaten this future, not only for scientific research but for breakthroughs that can improve the lives of patients and their families. It is perhaps ironic that at a time when legislation promises 'big and beautiful change,' it turns out one of the brain's smallest players may have the biggest impact on how we understand and remember our lives."

More information: David Clewett et al, Locus coeruleus activation "resets" hippocampal event representations and separates adjacent memories, *Neuron* (2025). DOI: 10.1016/j.neuron.2025.05.013
Journal information: Neuron
Provided by University of California, Los Angeles

Quantum computing occurs naturally in the human brain, study finds

Tryptophan-rich structures inside your cells might not just defend your body—they could be processing information using the strange speed and power of quantum mechanics. (

When a molecule of tryptophan absorbs ultraviolet light, it glows faintly as it lets off lower-frequency energy. This soft glow, known as fluorescence, is a familiar effect. But when many tryptophan molecules act together in well-organized

protein clusters, something unexpected happens. Their glow grows brighter and much faster than expected. This rare group behavior is called superradiance, and scientists now think it could reshape how we understand both life and information itself.

New research shows that certain proteins rich in tryptophan—especially those found in brain cells—might act as networks for quantum computing. These molecular systems seem to do more than just shield cells from damage. They may also process and send information with a speed and efficiency that outperforms known biological methods.

When Quantum Logic Defies the Noise

Quantum behaviors typically live in the cold and quiet. Quantum computers, for instance, must stay colder than outer space to avoid disruption. At room temperature, heat and noise usually destroy the fragile conditions required for quantum effects to survive. This has led most scientists to assume that such effects can't exist inside the body's warm and noisy environment.

A cell seen under microscope. (CREDIT: Fayette Reynolds M.S. / Pexels)© The Brighter Side of News

But living systems are busy, messy, and warm. Cells buzz with motion and energy. Proteins and neurons are far too bulky for classic quantum effects—or so it seemed. A group led by Philip Kurian at Howard University's Quantum Biology Laboratory has uncovered compelling evidence that quantum behavior doesn't just survive in biology—it may be essential to life itself.

Kurian's team discovered that dense networks of tryptophan molecules—packed into structures like microtubules, centrioles, and bundles of neurons—can act like quantum optical devices. These networks don't just carry light energy. They manage it in ways that mirror high-tech quantum systems, but inside living matter.

Their results, published in Science Advances, reveal that superradiance can emerge in warm biological tissue, not just in cold atomic systems. This breakthrough links quantum science with real-world biology. It suggests that the same effect seen in tightly controlled physics labs might also be part of how our bodies work at the smallest scale.

"This work connects the dots among the great pillars of twentieth century physics—thermodynamics, relativity, and quantum mechanics—for a major paradigm shift," said Kurian. The discovery hints that nature has long used quantum tools we're only beginning to understand—and it may have built life itself around them.

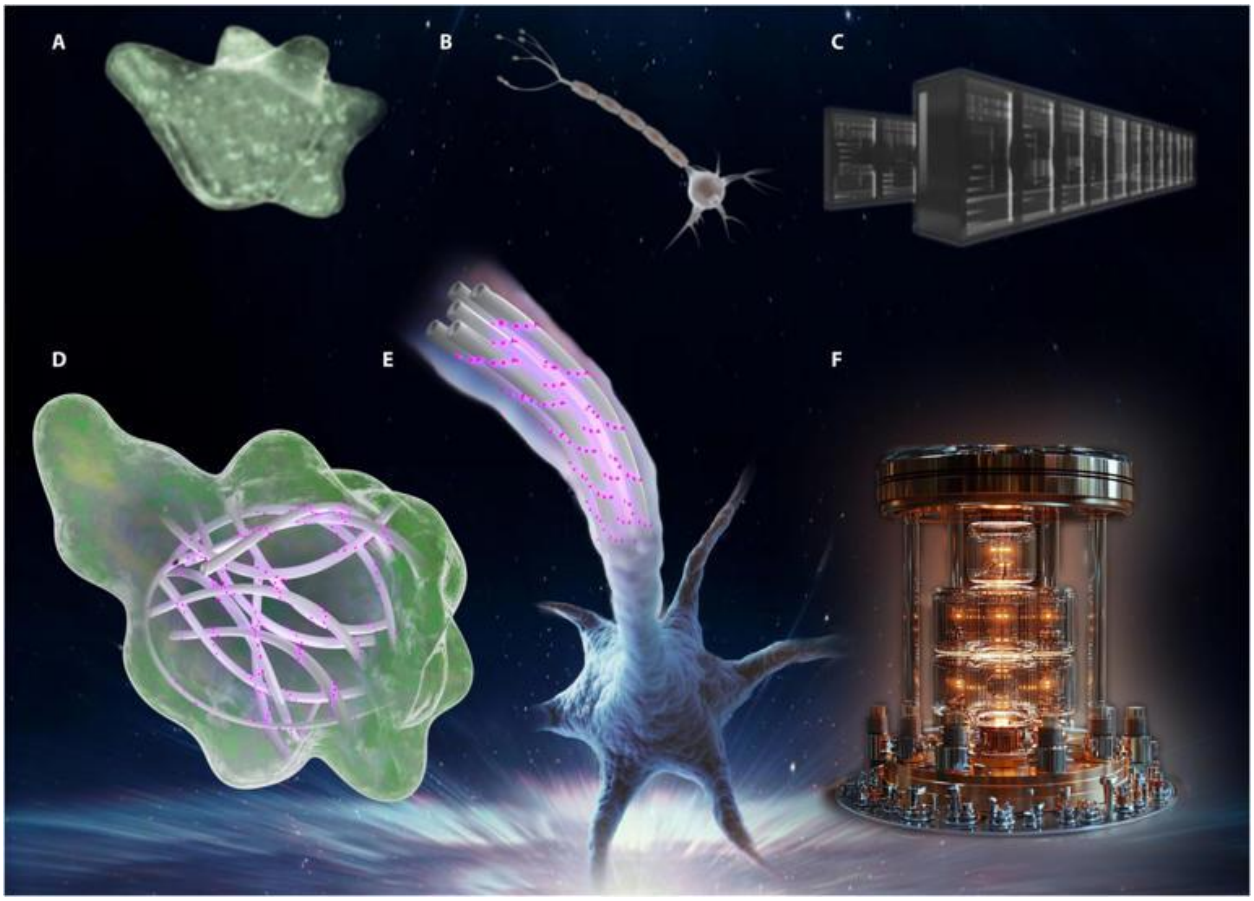
Why Tryptophan Is Special

Tryptophan is not just another amino acid. It has a unique indole ring structure, making it especially good at absorbing ultraviolet light. It also fluoresces with a strong Stokes shift, meaning the light it emits is clearly separated in color from the light it absorbs. These properties make it a favorite tool in laboratory studies of protein behavior.

But tryptophan isn't just helpful in a test tube. It appears naturally in key locations in living systems—often at the interface between water and lipids in cell

membranes. It's found in transmembrane proteins, photoreceptors, hemoglobin, and especially in the complex cytoskeletal structures inside cells. These include microtubules and centrioles, which help cells divide, change shape, and move.

Kurian's group studied these mesoscale networks—structures containing over 100,000 tryptophan molecules—and found that they often display a collective optical response. The more ordered the structure, the stronger the quantum effect. And even when they introduced disorder, the effects still survived under normal biological temperatures.



Living systems maintain information-processing architectures using photoexcited quantum degrees of freedom. (CREDIT: Science Advances)© The Brighter Side of News

Professor Majed Chergui of École Polytechnique Fédérale de Lausanne, who led the experimental team, explained: "It took very precise and careful application of standard protein spectroscopy methods, but guided by the theoretical predictions of our collaborators, we were able to confirm a stunning signature of superradiance in a micron-scale biological system."

How Living Systems May Use Quantum Light

Kurian's group believes these large tryptophan networks may have evolved to take advantage of their quantum properties. When cells breathe using oxygen—a process called aerobic respiration—they create free radicals, or reactive oxygen species (ROS). These unstable particles can emit high-energy UV photons, which damage DNA and other important molecules.

Tryptophan networks act as natural shields. They absorb this harmful light and re-emit it at lower energies, reducing damage. But thanks to superradiance, they may also perform this protective function much more quickly and efficiently than single molecules could.

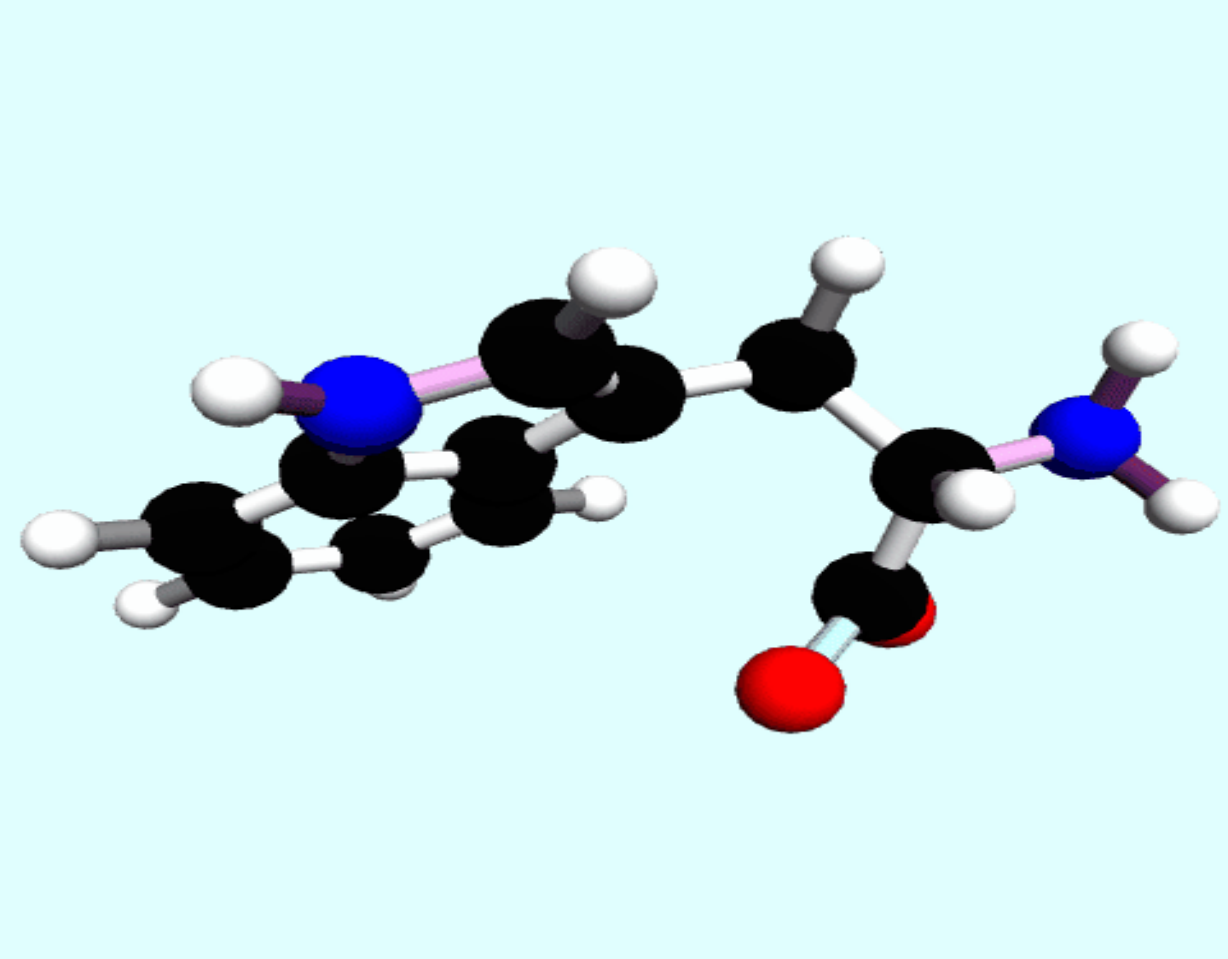
This speed could matter even more in the brain. Traditional neuroscience models say that information is passed between neurons using chemical signals, which take milliseconds to complete. But Kurian's study found that the superradiant signal transfer happens in picoseconds—about a billion times faster.

In a previous study, published in The Journal of Physical Chemistry, Kurian's team found that these signals might allow cells to share information at speeds and scales that traditional models can't explain. They could act like fiber optic cables, transmitting light-based data through tissues and enabling a new level of biological computing.

"This photoprotection may prove crucial in slowing or stopping degenerative illnesses," said Kurian. "We hope this will inspire a range of new experiments to understand how quantum-enhanced photoprotection plays a role in complex pathologies that thrive on highly oxidative conditions."

A New Kind of Computing

In his paper, Kurian took a bold step: he calculated how much information life on Earth may have processed since its beginning, based on the laws of quantum mechanics, the speed of light, and the density of matter in the universe. He found that life's information processing—powered by quantum-enhanced structures like tryptophan networks—might rival that of all known matter in the observable cosmos.



Tryptophan ball and stick model spinning. (CREDIT: CC BY-SA 4.0)© The Brighter Side of News

This finding echoes questions raised decades ago by physicist Erwin Schrödinger, who asked in his 1944 book *What is Life?* whether something deeper than chemistry might govern living systems. Kurian's work now offers a possible answer.

Professor Seth Lloyd of MIT, a pioneer in quantum computing, praised the study. "It's good to be reminded that the computation performed by living systems is vastly more powerful than that performed by artificial ones," he said.

Kurian's theories have attracted attention from quantum computing researchers around the world, including Professor Nicolò Defenu of ETH Zurich. "It's really intriguing to see a vital and growing connection between quantum technology and living systems," Defenu said.

Even space scientists are taking notice. Dante Lauretta, director of the Arizona Astrobiology Center, said that Kurian's predictions offer new insights into the

search for life elsewhere in the universe. "The remarkable properties of this signaling and information-processing modality could be a game-changer in the study of habitable exoplanets," he said.

Tryptophan-rich structures in your cells may be doing more than protecting you—they might be computing at quantum speeds.

Going Beyond the Brain

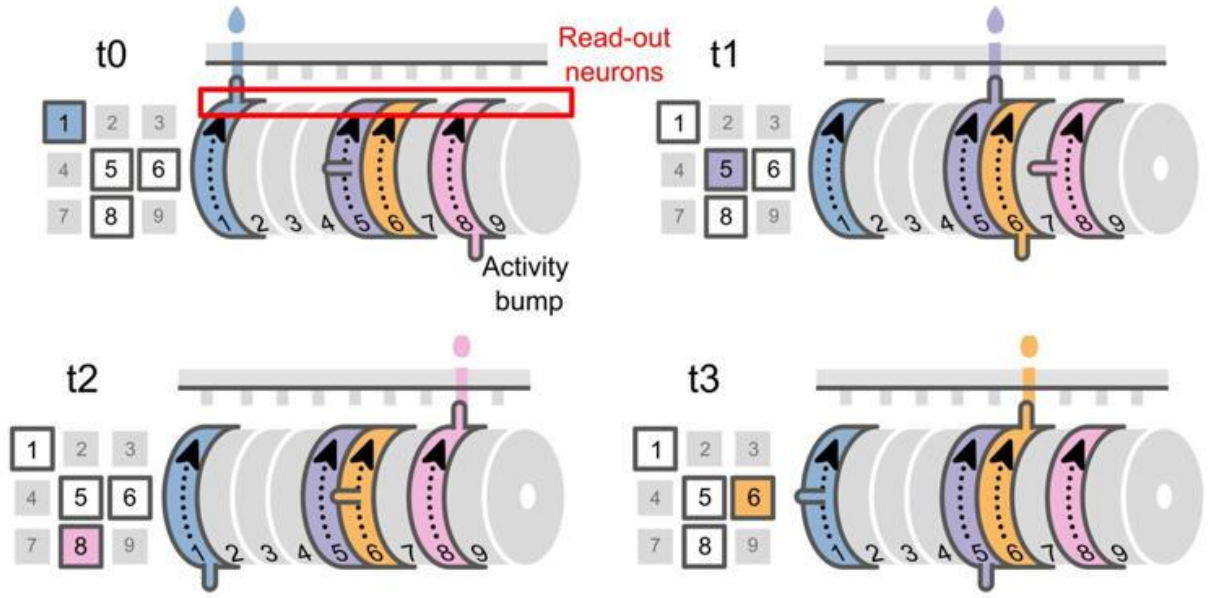
While most studies focus on neurons, Kurian and others remind us that most life on Earth is aneural. Bacteria, plants, fungi, and single-celled organisms form the bulk of the planet's biomass. These living systems may use tryptophan networks and quantum effects just as efficiently as brains do.

The presence of superradiant behavior in these simple organisms suggests that quantum information processing might be a core feature of life itself—not just an add-on for complex beings.

"There are signatures in the interstellar media and on interplanetary asteroids of similar quantum emitters," Lauretta said. "These may be precursors to eukaryotic life's computational advantage."

Kurian hopes this work will spark further research into the quantum dimensions of life. "In the era of artificial intelligences and quantum computers, it is important to remember that physical laws restrict all their behaviors," he said. "And yet, though these stringent physical limits also apply to life's ability to know and simulate the universe, we can still explore and make sense of it. It's awe-inspiring that we get to play such a role."

Neuroscientists reveal how cells in the brain form a coordinate system for behavioral sequences



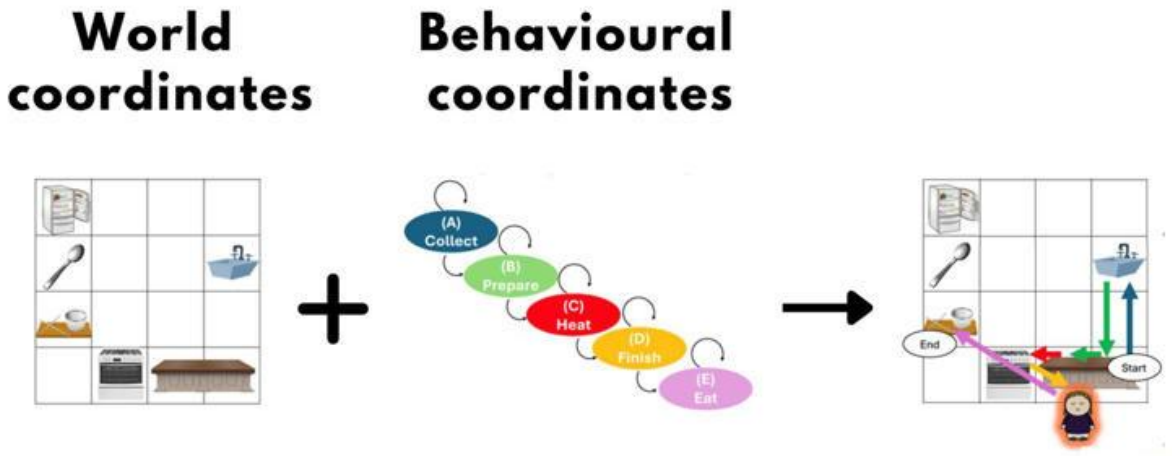
The brain acts like a music box in the way that it can be configured to play behavioral actions. Credit: Dr. Gil Costa.

Neuroscientists have discovered brain cells that form multiple coordinate systems to tell us "where we are" in a sequence of behaviors. These cells can play out different sequences of actions, just like a music box can be configured to play different sequences of tones.

The findings help us understand the algorithms used by the brain to flexibly generate complex behaviors, such as planning and reasoning, and might be useful in understanding how such processes go wrong in psychiatric conditions such as schizophrenia.

The research, published in *Nature,* outlines how scientists at the Sainsbury Wellcome Center at UCL and University of Oxford studied mice learning different behavioral sequences but with the same structure. This allowed the team to uncover how mice generalize structures to new tasks, a hallmark of intelligent behavior.

"Every day we solve new problems by generalizing from our knowledge. Take cooking, for example. When faced with a new recipe, you are able to use your background knowledge of similar recipes to infer what steps are needed, even if you have never made the meal before," said Dr. Mohamady El Gaby, first author on the study and postdoctoral neuroscientist in the Behrens lab at the Sainsbury Wellcome Center at UCL and Nuffield Department of Clinical Neurosciences, University of Oxford.



To solve the problem of how to cook a meal, the brain must combine world coordinates with behavioural coordinates. Credit: Dr. Matthew Nour.

"We wanted to understand at a detailed cellular level how the brain achieves this and also to infer from this brain activity the algorithms being used to solve this problem."

The researchers gave mice a series of four goal locations. While the details of the sequences were different, the general structure was the same. Mice moved between the goal locations (A B C and D) that repeated in a loop.

"After experiencing enough sequences, the mice did something remarkable—they guessed a part of the sequence they had never experienced before. When reaching D in a new location for the first time, they knew to go straight back to A. This action couldn't have been remembered, since it was never experienced in the

first place! Instead, it's evidence that mice know the general structure of the task and can track their 'position' in behavioral coordinates," explains Dr. El Gaby.

To understand how the mice learned the general structure of the task, the researchers used silicon probes that allowed them to record the activity of multiple individual cells from an area of the brain called the medial frontal cortex. They found that the cells collectively mapped the animal's "goal progress." For example, one cell could fire when the animal is 70% of the way to its goal, regardless of where the goal is or how far it takes to reach it.

"We found that the cells tracked the animal's behavioral position relative to concrete actions. If we think of the cooking analogy, the cells cared about progress towards subgoals such as chopping the vegetables. A subset of the cells were also tuned to map the progress towards the overall goal, such as finishing preparing the meal. The 'goal progress' cells therefore effectively act as flexible building blocks that come together to build a behavioral coordinate system," said Dr. El Gaby.

In effect, the team found that the cells form multiple coordinate systems, each telling the animal where it is relative to a specific action. In a similar way to a music box that can be configured to play any sequence of tones, the brain can instead "play" behavioral actions.

The team are now working to understand how these activity patterns are built into the brain's connections, both when learning new behaviors, and how they start to emerge in the developing brain. In addition, early work from the group and their collaborators suggests similar brain activity is present in equivalent circuits in healthy humans.

This has encouraged the team to work with psychiatrists to understand how these processes are affected in conditions like schizophrenia, which is known to involve the same brain circuits. This could help explain why people with schizophrenia overestimate their progress to goals leading to delusions.

More information: Mohamady El-Gaby, A cellular basis for mapping behavioural structure, *Nature* (2024). DOI: 10.1038/s41586-024-08145-x. www.nature.com/articles/s41586-024-08145-x

Provided by Sainsbury Wellcome Centre

How the brain stores 'unattended' information: Neuronal firing disproves activity-silent hypothesis JULY 29, 2025

by Ingrid Fadelli, Phys.org edited by Sadie Harley, reviewed by Robert Egan

Understanding how the human brain stores information and later uses it to complete various tasks has been a long-standing goal of neuroscience and psychology research. Past studies have identified different types of memory processes that have distinct roles and characteristics.

One of these, known as working memory, entails the storage and manipulation of important information for short periods of time, particularly information that is helpful for completing reasoning tasks or to make decisions in the short-term. Findings suggest that this temporary storage of information is associated with the continued and persistent firing of specific neurons in the brain.

Most past studies focusing on working memory processes relied on experimental tasks that require participants to prioritize and memorize all items they are presented with.

In contrast, very few have tried to understand how the human brain stores "unattended" items, or, in other words, stimuli that are momentarily not in focus and not immediately relevant for completing a task at hand.

Researchers at the Polish Academy of Sciences, SUNY Upstate Medical University, Military Hospital in Ełk and Wroclaw Medical University set out to test the validity of a theoretical model suggesting the existence of an "activity-silent" mechanism that is responsible for storing unattended memories.

Their findings, published in *Nature Human Behaviour*, disprove this theoretical prediction, instead showing that the brain's storage of unattended memories is also associated with the firing of neurons.

"We know that items in our working memory—our thoughts—are represented by the activity of specialized neurons," Jan Kaminski, senior author of the paper, told Medical Xpress.

"Whenever we need to maintain something in mind, specific neurons in our brain increase their firing rates. For instance, when memorizing a phone number, certain neurons temporarily become more active as they encode this information.

"Recent studies, however, have suggested that if a memory item is not actively attended to, the activity of these neurons drops back to baseline. For example, when we must remember a phone number but temporarily perform a different task."

Recent experimental evidence hinted at the possibility that unattended items are maintained in the brain via an activity-silent mechanism that is markedly different from the one supporting the storage of important information during working memory tasks. Nonetheless, most of this evidence was collected using non-invasive imaging techniques, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI).

Although EEG and fMRI are widely used to conduct neuroscience research, they both record the "average" activity of hundreds of thousands of neurons in the human brain. As a result, studies relying on these imaging techniques might have failed to pick up the activity of a few neurons, as it was averaged with the inactivity of several other neurons.

The average firing rate of cells coding information in working memory. The inset shows the firing rate reduced to three dimensions, indicating that items outside of attention differ not only from the no-memory condition but also from the in-focus attention condition. Credit: Paluch et al.

"Our lab specializes in directly recording neural activity during invasive clinical procedures, such as electrode implantation in the human brain for epilepsy monitoring," said Kaminski.

"This provides a unique opportunity to test the activity-silent hypothesis directly. As part of this study, we recorded from neurons in the temporal lobe known to be involved in working memory."

The participants who took part in the team's study were shown two images and asked to remember both images but focus on only one of them for the first part of the trial. Subsequently, they were either instructed to keep their attention on the same image or to shift their focus to the image that was previously unattended.

"This experimental design, known as the double retro-cue paradigm, has been employed in prior research," explained Katarzyna Paluch, first author of the paper.

"To record brain activity, we used an invasive clinical procedure called intracranial EEG, where electrodes are surgically placed directly into patients' brains for medical purposes, like epilepsy monitoring. This allowed us to record the activity of individual neurons."

Kaminski and his colleagues later examined the activity of neurons in the temporal lobe when participants shifted their attention to one or the other image. This allowed them to better understand how unattended images were stored in the brain.

"To our surprise, we found that even the image outside the focus of attention was still actively represented by neuronal firing," said Kaminski.

"This contradicts the activity-silent hypothesis and indicates that unattended items in working memory remain actively represented. Our findings suggest that a larger portion of our working memory—the mental workspace or 'mind's sketchpad'—is actively represented by neuronal activity."

The findings of this study suggest that thoughts and other information that is outside a person's immediate focus of attention is still represented by some neurons that remain active. In other words, the storage of this unattended information does not rely on activity-silent mechanisms, as some earlier works had suggested.

In addition to improving the present understanding of human memory processes, the results gathered by Kaminski and his colleagues could inform the future treatment of some psychiatric disorders that are sometimes accompanied by working memory deficits. These include attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD) and schizophrenia.

"For example, our findings raise the possibility of developing neural implants or electrical stimulators to help maintain specific information in working memory, expanding the scope of therapeutic interventions," added Kaminski.

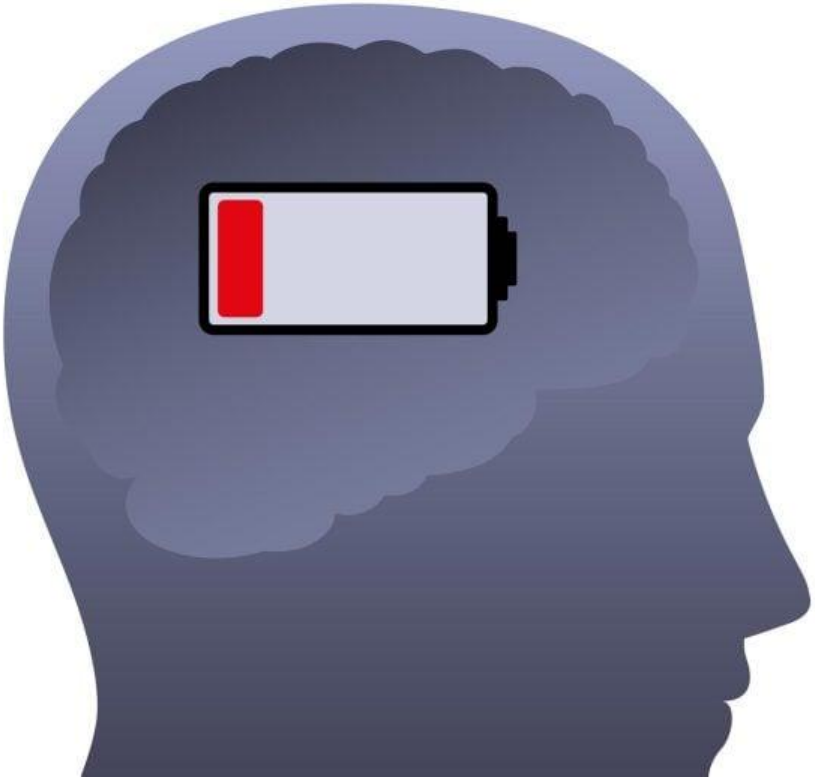
"Our lab is now continuing to focus on understanding working memory and its underlying neural mechanisms through direct recordings of neuronal activity in humans.

"In our future studies, we plan to explore how the brain switches between protecting current contents of working memory and encoding new information, which is critical for flexible cognitive functioning."

Written for you by our author Ingrid Fadelli, edited by Sadie Harley, and fact-checked and reviewed by Robert Egan—this article is the result of careful human work. We rely on readers like you to keep independent science journalism alive. If this reporting matters to you, please consider a donation (especially monthly). You'll get an **ad-free** account as a thank-you.
More information: K. Paluch et al, Unattended working memory items are coded by persistent activity in human medial temporal lobe neurons, *Nature Human Behaviour* (2025). DOI: 10.1038/s41562-025-02235-0.
Journal information: Nature Human Behaviour

How Recharging the Brain's "Batteries" Restored Lost Memory

BY INSERM (INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MÉDICALE)AUGUST 16, 2025



A new study shows that faulty mitochondria may be a root cause of dementia symptoms. Stimulating these cellular "powerhouses" in mice restored memory, offering a potential new approach to treating neurodegenerative diseases. Credit: Shutterstock

Mitochondria are tiny structures inside our cells that supply the energy our bodies need to survive, and scientists are steadily uncovering more about how they work. A new study in *Nature Neuroscience*, led by researchers at Inserm and the University of Bordeaux's NeuroCentre Magendie in partnership with the Université de Moncton in Canada, has for the first time shown a direct cause-and-effect relationship between malfunctioning mitochondria and the cognitive problems linked to neurodegenerative diseases.

Using a newly developed, highly specialized tool, the team was able to boost mitochondrial activity in animal models of neurodegenerative disorders. This intervention led to noticeable improvements in memory deficits. Although these findings are preliminary, they point to mitochondria as a promising focus for future therapies.

Why Brain Cells Depend on Mitochondria

A mitochondrion is a small structure within cells that generates the energy needed for normal cellular activity. The brain consumes an enormous amount of energy, and its neurons depend on the power produced by mitochondria to send signals to one another. When mitochondrial performance falters, neurons lose the energy required to work properly.

Neurodegenerative diseases gradually disrupt how neurons function and ultimately lead to their death. In Alzheimer's disease, for instance, the decline of neurons before cell death occurs is often accompanied by reduced mitochondrial activity. Until now, the lack of effective tools has made it difficult to determine whether this mitochondrial decline actually contributes to the disease process or merely results from it.

A Groundbreaking Experimental Tool

In this latest research, scientists from Inserm and the University of Bordeaux, working with colleagues at the Université de Moncton, created a novel method to temporarily increase mitochondrial activity. They reasoned that if stimulating mitochondria improved symptoms in animals, it would indicate that the loss of mitochondrial function happens before neurons die in neurodegenerative disease.

Targeting G Proteins to Restore Brain Function

In previous studies, the research teams already described the specific role of G proteins[1] in the modulation of mitochondrial activity in the brain. In the present paper, the researchers succeeded in generating an artificial receptor, called mitoDreadd-Gs, able to activate G proteins directly in the mitochondria, thereby stimulating mitochondrial activity. The stimulation of mitoDreadd-Gs in the brain led to the normalisation of both mitochondrial activity and memory performance of dementia mouse models.

"This work is the first to establish a cause-and-effect link between mitochondrial dysfunction and symptoms related to neurodegenerative diseases, suggesting that impaired mitochondrial activity could be at the origin of the onset of neuronal degeneration," explains Giovanni Marsicano, Inserm research director and co-senior author of the study.

Looking Ahead to New Therapies

"These results will need to be extended, but they allow us to better understand the important role of mitochondria in the proper functioning of our brain. Ultimately, the tool we developed could help us identify the molecular and cellular mechanisms responsible for dementia and facilitate the development of effective therapeutic targets," explains Étienne Hébert Chatelain, professor at the Université de Moncton and co-senior author of the study.

“Our work now consists of trying to measure the effects of continuous stimulation of mitochondrial activity to see whether it impacts the symptoms of neurodegenerative diseases and, ultimately, delays neuronal loss or even prevents it if mitochondrial activity is restored,” added Luigi Bellocchio, Inserm researcher and co-senior author of the study.

Notes

1. G-proteins have the specific role of enabling the transfer of information within cells.

Reference: “Potentiation of mitochondrial function by mitoDREADD-G_s reverses pharmacological and neurodegenerative cognitive impairment in mice” by Antonio C. Pagano Zottola, Rebeca Martín-Jiménez, Gianluca Lavanco, Geneviève Hamel-Côté, Carla Ramon-Duaso, Rui S. Rodrigues, Yamuna Mariani, Mehtab Khan, Filippo Drago, Stephanie Jean, Itziar Bonilla-Del Río, Daniel Jimenez-Blasco, Jon Egaña-Huguet, Abel Eraso-Pichot, Sandra Beriain, Astrid Cannich, Laura Vidal-Palencia, Rosmara Infantino, Francisca Julio-Kalajzić, Doriane Gisquet, Ania Goncalves, Inas Al-Younis, Yann Baussan, Stephane Duvezin-Caubet, Anne Devin, Edgar Soria-Gomez, Nagore Puente, Juan P. Bolaños, Pedro Grandes, Sandrine Pouvreau, Arnau Busquets-Garcia, Giovanni Marsicano, Luigi Bellocchio and Etienne Hebert-Chatelain, 11 August 2025, *Nature Neuroscience*.
DOI: 10.1038/s41593-025-02032-y

Fascinating new neuroscience study shows the brain emits light through the skull

A new study published in *iScience* provides evidence that the human brain emits extremely faint light signals that not only pass through the skull but also appear to change in response to mental states. Researchers found that these ultraweak light emissions could be recorded in complete darkness, and they appeared to shift in response to simple tasks like closing the eyes or listening to sound. The findings suggest that this faint brain light may carry information about brain activity—possibly opening the door to a new way of studying the brain (photoencephalography).

All living tissues release tiny amounts of light during normal metabolism, known as ultraweak photon emissions. This happens when excited molecules return to a lower energy state and emit a photon in the process. The light is incredibly faint—about a million times weaker than what we can see—and falls within the visible to near-infrared range. In contrast to bioluminescence, which involves specific chemical reactions like those used by fireflies, ultraweak photon emissions happen constantly in all tissues, without special enzymes or glowing compounds.

The brain emits more of this faint light than most other organs because of its high energy use and dense concentration of photoactive molecules. These include compounds like flavins, serotonin, and proteins that can absorb and emit light. Photon emission rates also seem to rise during oxidative stress and aging and may reflect changes in cell health or communication.

The research team, led by Hayley Casey, Nirosha Murugan, and colleagues at Algoma University, Tufts University, and Wilfrid Laurier University, wanted to know if these faint light emissions could be used to monitor brain activity. Unlike other imaging methods that require stimulation—such as strong magnetic fields or infrared light—measuring UPEs is entirely passive. That means it doesn't introduce anything new to the brain.

The researchers proposed that UPEs might offer a new way to monitor brain function safely and without interference, similar to how EEG tracks electrical brain waves without applying energy. They also wanted to test whether UPEs reflect mental states like resting with eyes closed or responding to sound, and whether these signals match known changes in electrical brain rhythms.

The researchers recruited 20 healthy adult participants and measured both UPEs and brain electrical activity while the participants sat in a dark room. The setup included photomultiplier tubes placed near the occipital and temporal regions of the head, where the brain processes visual and auditory information. A third sensor recorded background light. At the same time, participants wore a cap with electroencephalography sensors to record electrical brain rhythms.

Participants went through a ten-minute recording session that included five conditions. First, they sat with eyes open and then with eyes closed. Next, they listened to a simple repeating auditory stimulus, followed by another eyes-closed period, and finally another eyes-open period. The aim was to see whether brain UPEs responded to known manipulations of brain activity, particularly the shift in alpha rhythms that occurs when people close their eyes.

Photon emissions were recorded in short time intervals and analyzed for variability, frequency content, and stability over time. The team compared the results to background signals and examined correlations with electrical brain rhythms recorded at the same time.

The researchers found that the light emitted from the brain could be distinguished from background light based on its variability and complexity. Brain UPEs showed greater entropy and a more dynamic signal than background recordings. These emissions also showed a distinctive frequency profile below 1 Hz, meaning that the light fluctuated in slow rhythmic patterns roughly once every one to ten seconds. This signature was not present in the background light and was especially pronounced in the occipital region.

The researchers also observed that brain UPEs appeared to reach a steady state during each task, particularly by the end of the two-minute recording segments. These stable patterns shifted when participants moved between eyes-open and eyes-closed conditions, suggesting that the emissions reflect changes in the brain's internal state. However, the direction of change was not consistent across all participants, possibly reflecting individual differences or the complexity of the underlying metabolic processes.

When the researchers compared UPEs to brain electrical rhythms, they found modest correlations. For instance, alpha rhythms—often associated with relaxed wakefulness and increased during eyes-closed states—correlated with photon emissions from the occipital region, but only when the participants' eyes were closed. They also found some associations between UPE variability and temporal lobe rhythms during auditory stimulation. Still, the relationships were not strong, and many expected correlations did not emerge, highlighting the need for further research.

While the findings are promising, the authors caution that this was a preliminary study with several limitations. The sample size was small, and the recording equipment only covered a few areas of the head. The sensors also detected a wide range of wavelengths, which may have obscured more specific light patterns. More precise filters or detectors could help uncover wavelength-specific signatures related to different brain functions.

The researchers also suggest that expanding the sensor array could improve spatial resolution and help identify the origins of UPEs within the brain. Because these emissions are tied to metabolic activity, they may come from a variety of cell types, including neurons and glial cells, and from different depths in the brain. Developing methods to localize these signals will be an important next step.

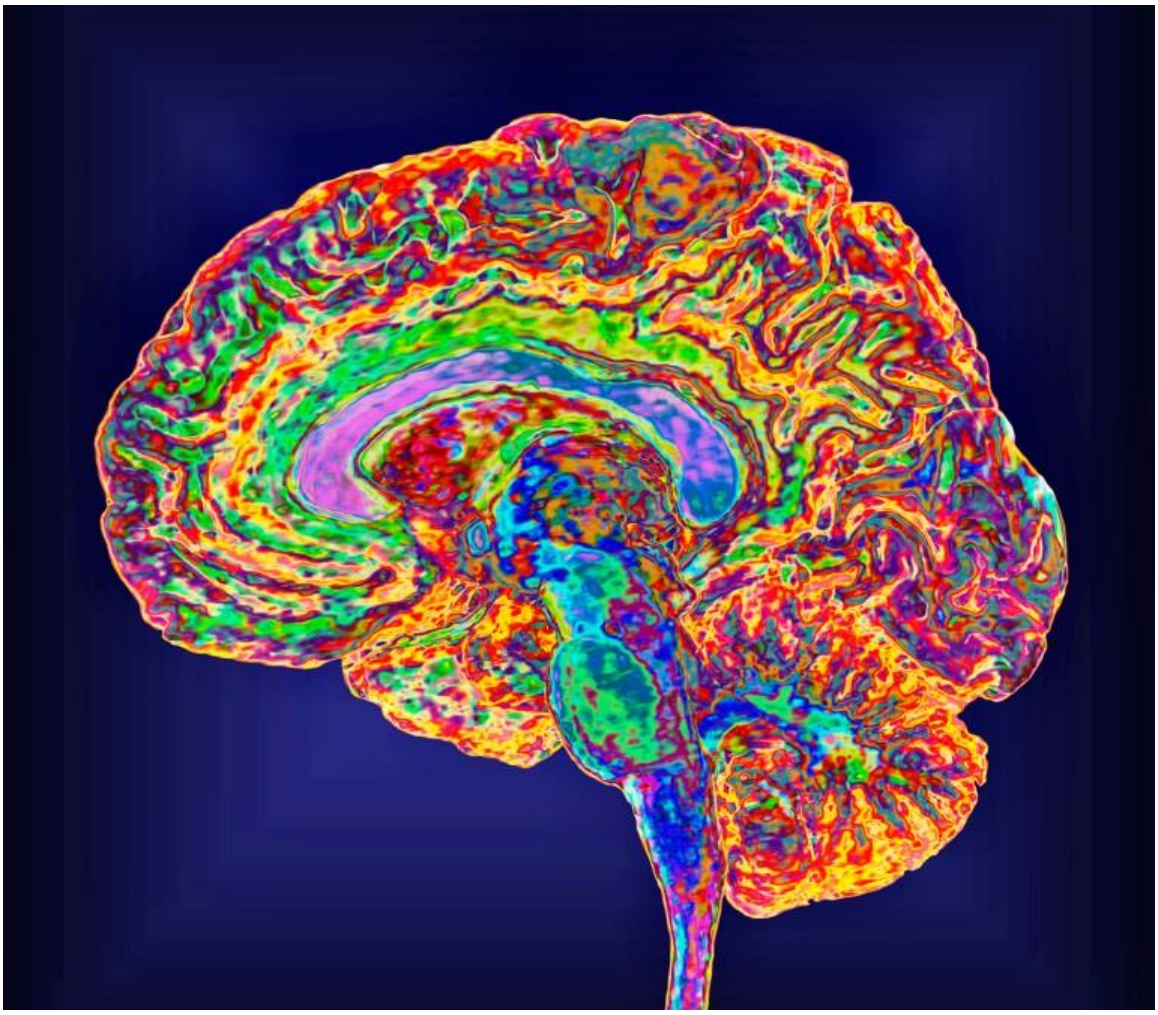
The study did not include measurements from other parts of the body, which could help clarify whether similar light emissions occur in non-brain tissues and how they differ. Including more participants and exploring variations based on age, sex, or health status may also reveal meaningful patterns. In the future, machine learning and advanced imaging techniques may allow researchers to decode UPE patterns and use them to detect brain disorders or monitor brain health.

"We view the current results as a proof-of-concept demonstration that patterns of human-brain-derived UPE signals can be discriminated from background light signals in darkened settings despite very low relative signal intensity," the researchers wrote. "Photoencephalography would be maximally non-invasive (i.e., passive recording) with high temporal resolution, like EEG or MEG; however, the measurement of UPEs would be linked to oxidative metabolism with several clinical applications described elsewhere. Future studies may find success in using select filters and amplifiers to sieve and enhance UPE signal features from healthy and diseased brains."

The study, "Exploring ultraweak photon emissions as optical markers of brain activity," was authored by Hayley Casey, Isabella DiBerardino, Mattia Bonzanni, Nicolas Rouleau, and Nirosha J. Murugan.

A mind-reading brain implant that comes with password protection 14 August 2025

A brain–computer interface decodes in near-real time the imagined speech of people who have difficulty enunciating words.



A brain scan (artificially coloured) produced by magnetic resonance imaging. Credit: K H Fung/Science Photo Library

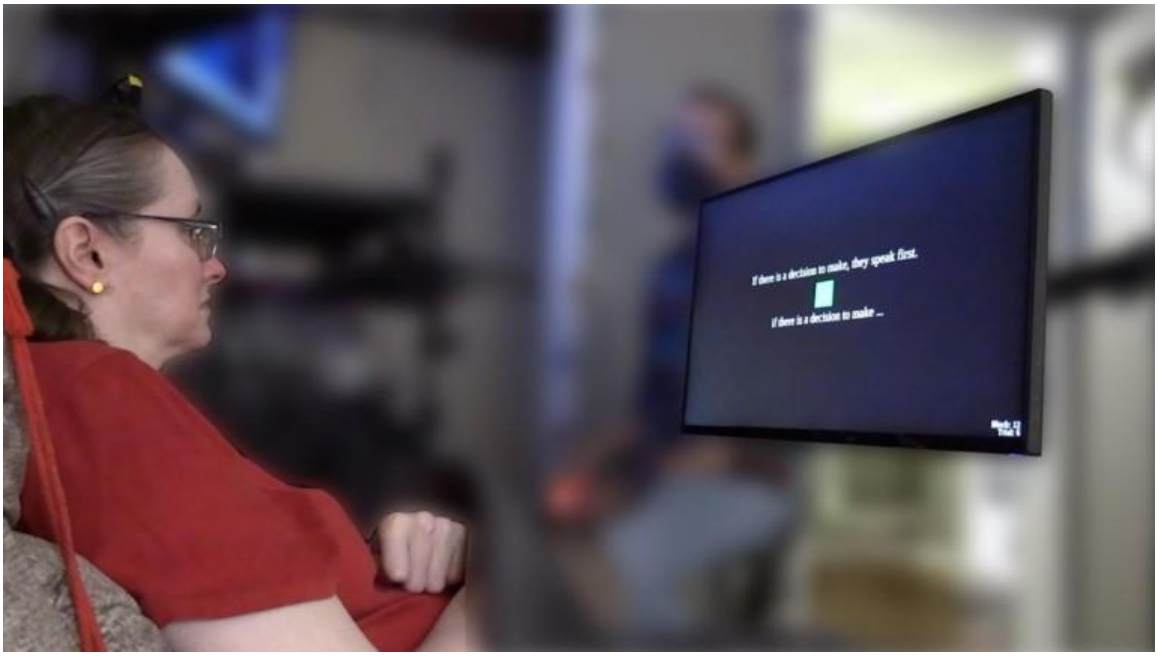
A brain implant can decode a person's internal chatter — but the device works only if the user thinks of a preset password[1].

The mind-reading device, or brain–computer interface (BCI), accurately deciphered up to 74% of imagined sentences. The system began decoding users' internal speech — the silent dialogue in people's minds — only when they thought of a specific keyword. This ensured that the system did not accidentally translate sentences that users would rather keep to themselves.

The study, published in *Cell* on 14 August, represents a “technically impressive and meaningful step” towards developing BCI devices that accurately decode internal speech, says Sarah Wandelt, a neural engineer at the Feinstein Institutes for Medical Research in Manhasset, New York, who was not involved in the work. The password mechanism also offers a straightforward way to protect users’ privacy, a crucial feature for real-world use, adds Wandelt.

Avoiding eavesdropping

BCI systems translate brain signals into text or audio and have become promising tools for restoring speech in people with paralysis or limited muscle control. Most devices require users to try to speak out loud, which can be exhausting and uncomfortable. Last year, Wandelt and her colleagues developed the first BCI for decoding internal speech, which relied on signals in the supramarginal gyrus, a brain region that plays a major part in speech and language[2].



A study participant who has trouble speaking clearly because of a stroke uses the brain–computer interface.Credit: Emory BrainGate Team

But there’s a risk that these internal-speech BCIs could accidentally decode sentences users never intended to utter, says Erin Kunz, a neural engineer at Stanford University in California. “We wanted to investigate this robustly,” says Kunz, who co-authored the new study.

First, Kunz and her colleagues analysed brain signals collected by microelectrodes placed in the motor cortex — the region involved in voluntary movements — of four participants. All four have trouble speaking, one because of a stroke and three because of motor neuron disease, a degeneration of the nerves that leads to loss of muscle control. The researchers instructed participants to either attempt to say a set of words or imagine saying them.

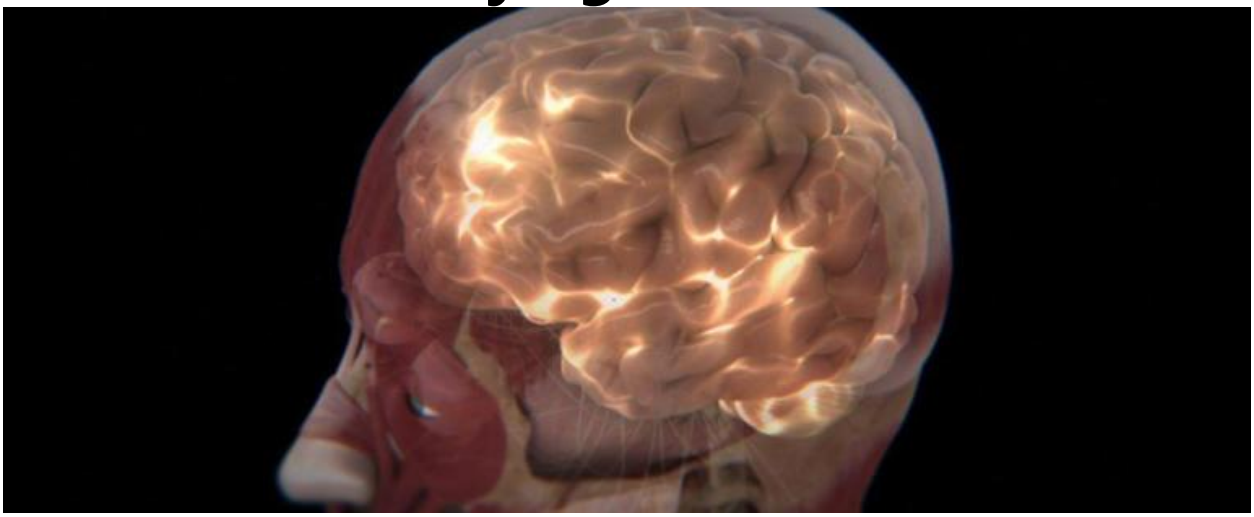
Recordings of the participants' brain activity showed that attempted and internal speech originated in the same brain region and generated similar neural signals, but those associated with internal speech were weaker.

Brain implant translates thoughts to speech in an instant

Next, Kunz and her colleagues used this data to train artificial-intelligence models to recognize phonemes, the smallest units of speech, in the neural recordings. The team used language models to stitch these phonemes together to form words and sentences in real time, drawn from a vocabulary of 125,000 words.

The device correctly interpreted 74% of sentences imagined by two participants who were instructed to think of specific phrases. This level of accuracy is similar to that of the team's earlier BCI for attempted speech, says Kunz.

Your Brain Emits a Secret Light That Scientists Are Trying to Read



Your Brain Emits a Secret Light That Scientists Are Trying to Read

Many of Earth's critters have the ability to emit a visible glow, but humans aren't usually considered among their number.

This may not be entirely correct. Going all the way back to 1923, a number of studies have found humans luminesce in frequencies that would be visible if they weren't too faint for us to actually see. From the moment of conception until we shuffle off this mortal coil, we literally shine.

It's controversial, absolutely, but it's possible that detecting these 'biophotons' could tell us a thing or two about what takes place beneath our skin.

In a new study, a team of researchers led by biologist Hayley Casey of Algoma University in Canada has investigated the extremely weak glow of one lump of tissue in particular: the brain that resides inside the skull of every living human. They carefully recorded the faint glow of the human brain from *outside* the skull, and found that it changes according to what the brain is doing.

This, they say, offers an exciting new possibility for gauging brain health: a yet-to-be-developed technique they call photo encephalography.

frameborder="0" allow="accelerometer; autoplay; clipboard-write; encrypted-media; gyroscope; picture-in-picture; web-share" referrerpolicy="strict-origin-when-cross-origin" allowfullscreen>

"As the first proof-of-concept demonstration that ultraweak photon emissions (UPEs) from human brains can serve as readouts to track functional states, we measured and characterized photon counts over the heads of participants while they rested or engaged in an auditory perception task," they write in their paper.

"We demonstrated that brain-derived UPE signals can be distinguished from background photon measures. Additionally, our results suggest that for a given task, the UPE count may reach a stable value."

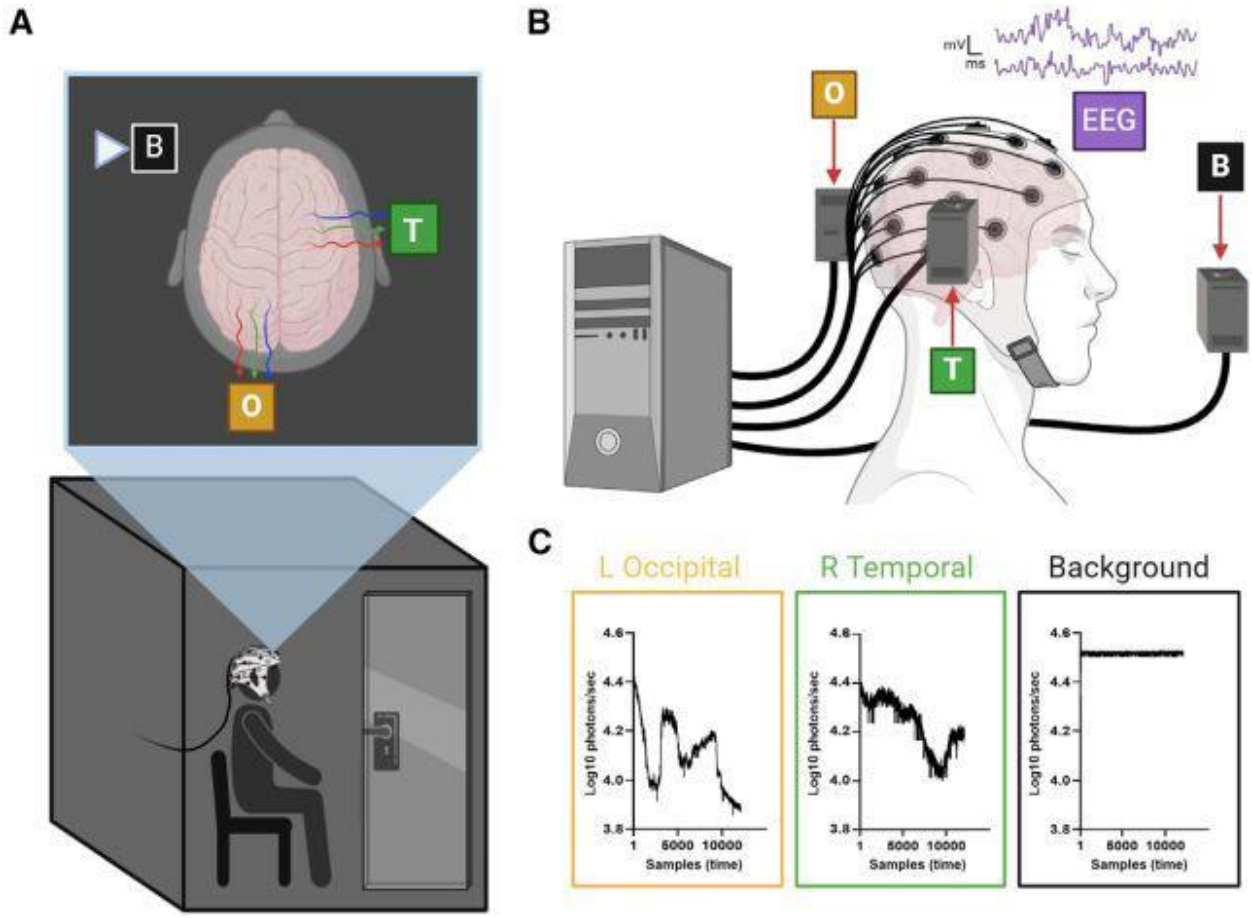
Everything in the Universe with a temperature higher than absolute zero – humans included – emits a type of infrared radiation called thermal radiation. When we talk about UPEs, it is a distinct phenomenon from thermal radiation.

UPEs are emitted in near-visible to visible wavelength bands, and are the result of electrons emitting photons as they lose energy, a normal by-product of metabolism.

Casey and her colleagues sought to conclusively distinguish brain UPEs from background radiation, and determine whether these UPEs exhibit patterns consistent with different levels of brain activity.

They placed each of their study participants in a dark room. An electroencephalography (EEG) cap was placed on the participant's head to monitor their brain activity, and photomultiplier tubes were positioned around them to record any light emissions. These are extremely sensitive vacuum tubes that can detect even the very faintest light.

Then, the participants were recorded at rest, and performing sound-based tasks (so they could do them in the dark). The results showed not just that UPEs are real and measurable even from outside the participants' heads – there was also a clear correlation between UPE output and the activity registered by the EEG cap.



A diagram of the experimental setup and the results. (Casey et al., Curr. Biol. , 2025)

Future work, the researchers say, could delve into how neuroanatomy might impact UPE output, as well as how different activities manifest in patterns of UPEs, rather than just the two states of brain rest and brain activity.

We also don't know if each individual has a UPE 'fingerprint' that would need to be recorded as a baseline against which to measure anomalous activity.

"We view the current results as a proof-of-concept demonstration that patterns of human-brain-derived UPE signals can be discriminated from background light signals in darkened settings despite very low relative signal intensity," the researchers write.

"Future studies may find success in using select filters and amplifiers to sieve and enhance UPE signal features from healthy and diseased brains."

The paper has been published in *Current Biology*.

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Exploring ultraweak photon emissions as optical markers of brain activity

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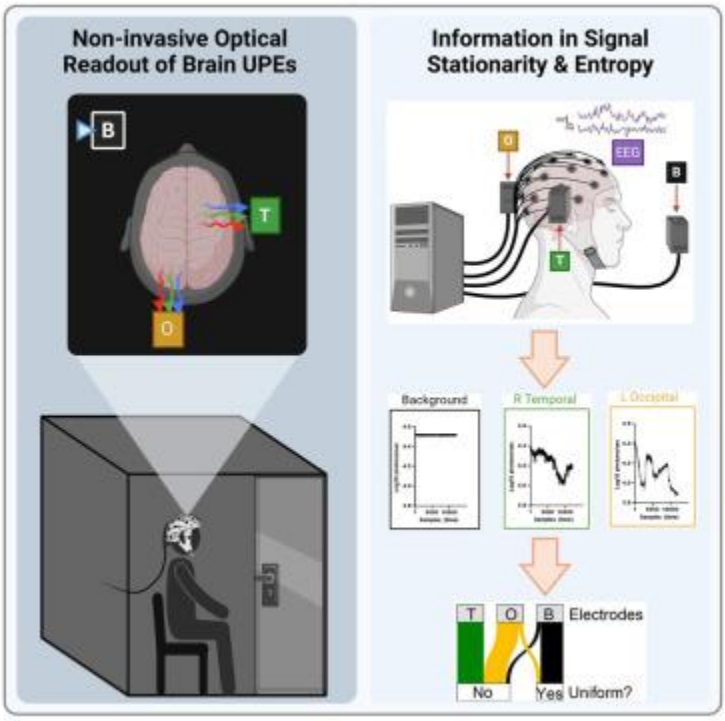
Highlights

- Ultraweak photon emissions (UPEs) were detected in resting and active human brains
- Brain UPE spectra and entropy vary by task, diverging from background levels
- Optical readouts correlate with evoked neuroelectric oscillations across tasks
- Label-free photoencephalography represents a novel method for brain monitoring

Summary

Brains are highly metabolic organs that emit ultraweak photon emissions (UPEs), which predict oxidative stress, aging, and neurodegeneration. UPEs are triggered by neurotransmitters and biophysical stimuli, but they are also generated by cells at rest and can be passively recorded using modern photodetectors in dark environments. UPEs play a role in cell-to-cell communication, and neural cells might even have waveguiding properties that support optical channels. However, it remains uncertain whether passive light emissions can be used to infer brain states as electric and magnetic fields do for encephalography. We present evidence that brain UPEs differ from background light in spectral and entropic properties, respond dynamically to tasks and stimulation, and correlate moderately with brain rhythms. We discuss these findings in the context of other neuroimaging methods, the potential of new measurement parameters, the limitations of light-based readouts, and the possibility of developing a platform to readout functional brain states: photoencephalography.

Graphical abstract



Subject areas

1. Cognitive neuroscience
2. Neuroscience

Introduction

Cells and tissues are traditionally understood to communicate through molecules and gene transcription. However, an emerging dimension of biophysical signaling is gaining attention. It is well established that cells and tissues can communicate via electrical signals, particularly in the brain and heart. Increasingly, evidence points to the role of light signals, in the form of ultraweak photon emissions (UPEs), as being physiologically relevant and potentially useful as indicators of both healthy and diseased states.[1,2] These UPEs were first described as “mitogenic radiation” by Alexander Gurwitsch in 1923, following his pioneering experiments that demonstrated that onion roots could stimulate growth in nearby conspecifics, even when separated by glass barriers, but not by quartz.[3] Subsequent studies corroborated the involvement of endogenous ultraviolet (UV) light as the mediating factor for this growth induction,[4] highlighting the potential role of biophotonic signals in cellular communication and development.

This phenomenon has since been replicated in diverse uni- and multicellular organisms,[5,6,7,8] and due in part to the development of technologies such as photomultiplier tubes (PMT), single-photon counters (SPC), and charge-coupled devices (CCD), much has been learned about UPEs. Indeed, biological tissues

continuously emit very low intensity light (~10^{-16} W/m^2, a few thousand photons per cm^2 per second)[9] within the visible-to-near-visible spectral range (200–900 nm). UPEs are generated by radiative decay of excited molecules and reflect the metabolic states of cells, correlating with the production of reactive oxygen species (ROS).[2] Consistent with the periodicities of hormonal fluctuations and oxidative metabolism, UPEs display diurnal and seasonal variations[10,11,12] and are coupled to mitochondrial respiration, of which ROS is a primary byproduct.[13] However, UPEs can also be evoked by ligand-receptor interactions[14] or by recent exposures to external light sources,[15,16] suggesting both endogenous and delayed re-emission mechanisms. Notably, UPEs are distinct from blackbody radiation, which is orders of magnitude less intense, and bioluminescence, which is typically more intense but related to specific biochemical reactions (e.g., luciferase in fireflies, jellyfish).[17] Despite these advances and an emerging science of UPEs as participants in cellular communication,[2,18] limited practical applications have been implemented to date.

Neural tissues have received special attention as a source of UPEs due to their excitable physiology, high metabolic load,[19,20] and marked sensitivity to light stimulation.[21,22,23] Indeed, the wavelengths of resting and glutamate-induced UPEs shift significantly as a function of aging[24,25,26,27,28] and cognitive potential.[29] Several investigators have hypothesized and successfully modeled optical neurotransmission, suggesting a role of myelinated nerve fibers as waveguides for UPE-based communication channels in the brain.[30,31] Thus, in addition to synaptic transmission, gap junctions, and ephaptic couplings, there is evidence to indicate that brain tissues display photonic transmission as a signaling modality. That neural cells express a diversity of photoactive molecules, including non-visual opsins (e.g., OPN3 or “encephalopsin”), auto-fluorescent neurotransmitters (e.g., serotonin), and flavins (e.g., cryptochrome) suggests that UPEs may serve recondite functions that could be leveraged to develop label-free *in vivo* imaging techniques.[32]

Current functional neuroimaging approaches use ionizing radiation (e.g., positron-emission tomography or PET), high-intensity magnetic fields (e.g., functional magnetic resonance imaging or fMRI), and near-infrared light (e.g., functional near-infrared spectroscopy or fNIRS) to resolve functional brain states. Although fNIRS and fMRI are relatively non-invasive compared to PET, brain tissues are highly responsive to magnetic fields[32] as well as infrared and near-infrared wavelengths of light (650–950 nm), which can suppress or enhance neurotransmission[33,34,35,36] and neural oscillations,[37,38] thus complicating interpretations of functional readouts. Whereas many functional imaging techniques involve the application of activity-inducing stimulation by the instrument itself, some including electroencephalography (EEG) and magnetoencephalography (MEG) are fully passive.[39]

Analogous to the passive measurement of microvolt fluctuations over the scalp associated with EEG, we hypothesized that passive measurement of brain UPEs would be maximally non-invasive and non-confounding. That is, since no external stimulus is applied, which might induce or suppress neural activity, imaging would be safe and unperturbed. Passive measurement would also enable the identification of relationships between ambient electromagnetic stimuli in the environment and brain activity. Further, because EEG profiles can be predictably altered without the use of optical stimuli, either by auditory stimulation or by simply closing one’s eyes (i.e., 10 Hz “alpha-generating”),

UPEs may be measured simultaneously. Here, we sought to characterize UPE patterns detected from human brains while the participants engaged in tasks that are known to affect brain activity as measured by conventional neuroimaging devices such as quantitative EEG (qEEG). UPEs over the occipital and temporal lobes were distinguished from background measurements as a function of signal variability, entropy, and stationarity. Temporal dynamics of brain, but not background UPEs, also changed as a function of task, suggesting a potential application of passive brain light recordings. Some associations were identified between neural oscillations and brain UPEs; however, several parameters are discussed that should be considered when interpreting biological relevance, to optimize functional readouts, and to determine suitability for imaging applications or as a support of existing neuroimaging techniques.

Results

Brain UPE signals can be distinguished from the background signal

Although UPEs have been previously linked to brain functions,[26,40,41] it is yet to be determined whether human brain UPE signals can be distinguished from local background photon noise across several signal parameters. We investigated whether UPE recordings over the left occipital and right temporal lobes (five tasks, 2 min each as outlined in the STAR Methods section) exhibited a distinct signature compared to background UPE signals (Figure 1).

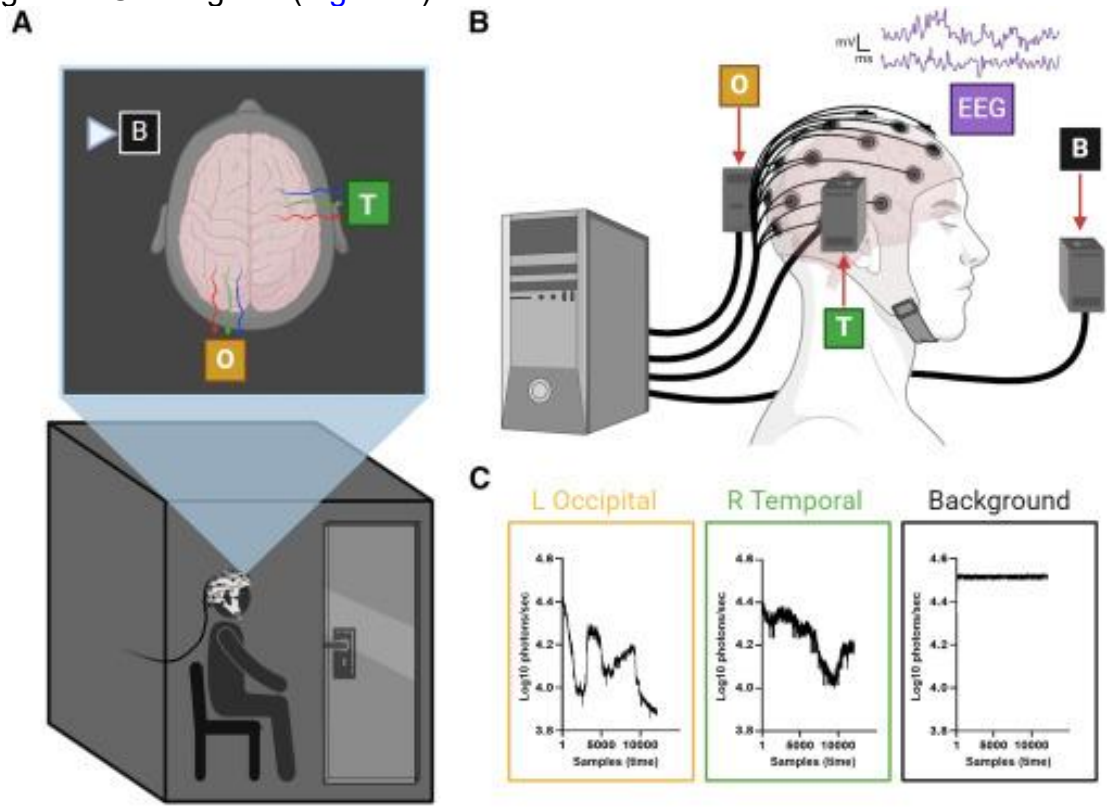


Figure 1 qEEG and UPE recordings were collected simultaneously from human participants

As seen in Figure 2A, normalized UPE counts were plotted over time for each combination of subject and PMT (B: Background; O: Occipital; T: Temporal; Subject ID: 1:20). Using a hierarchical clustering approach, we computed the pairwise distances between PMTs for each subject (Figure 2B, left) as a proxy of UPE signal similarity. We hypothesized that brain signals (occipital and temporal) would exhibit more similar UPE temporal dynamics (lower pairwise distance) compared to background signals. Accordingly, the pairwise distance was significantly lower for the Occipital-Temporal (O-T) pair compared to either Background-Occipital (B-O) or Background-Temporal (B-T) pairs. We then computed the coefficients of variation (CVs; Figure 2B, central) and entropy values (Figure 2B, right) for each raw UPE trace as a proxy of signal variability and complexity, respectively. Both the Occipital and Temporal UPE signals showed increased signal variability (CV) and complexity (entropy) compared to Background UPE traces.

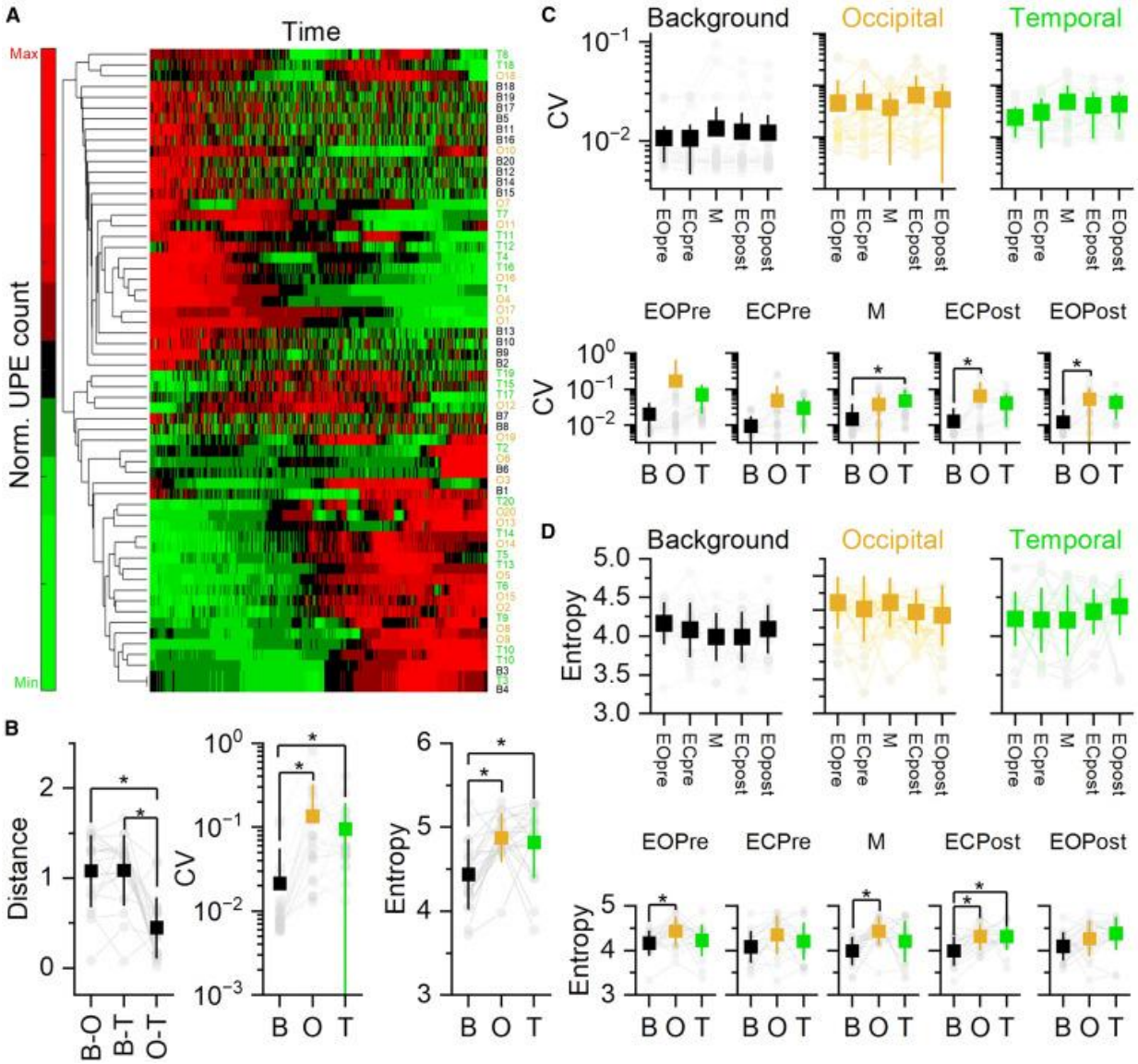


Figure 2 Brain UPE signals possessed distinct temporal dynamic, increased variability, and complexity

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These results revealed that brain-derived UPE signals had a distinct temporal dynamic compared to background photon signals, exhibiting greater similarity to each other than when compared to local background signals and had increased entropic content and variability.

Entropy and UPE trace variability remain consistent across tasks and weakly distinguish between PMTs for a given task

We then investigated whether CV and entropy varied as a function of the task (Eyes Open pre, Eyes Closed pre, Music, Eyes Closed post, and Eyes Open post; pre and post refers to the Music task). CV and entropy (Figures 2C and 2D, respectively) are shown for each PMT across tasks or for each task across PMTs. For all the PMTs, both CV and entropy showed no significant changes across tasks (See Table S1). With few exceptions distinguishing between background and brain UPE signals, CV and entropy were not different between PMTs for a given task. These results showed that neither entropy nor CV changed across tasks within PMTs and that they only weakly distinguished between background vs. brain UPE signals for some tasks.

A distinct brain spectral frequency pattern, independent of specific tasks, distinguishes occipital UPE signals from background signals

Rhythmic activities are essential for brain function and have defined analytical approaches to understanding brain states associated with sleep, attention, memory, and other cognitive features.[42] Therefore, we explored whether brain UPE signals exhibit distinct frequency patterns compared to background signals.
Representative spectrograms and averaged power spectra graphs for each PMT are shown in Figures 3A and 3B, respectively. After visual inspection of the averaged power spectra, we binned the frequency range into three bands: Band1 (0.1–0.3 Hz), Band2 (0.3–1 Hz), and Band3 (1–10 Hz). Since the power for each band did not significantly change neither over time nor across PMTs (Table S1), we averaged the power over time for each band and plotted it across PMTs (Figure 3C). The averaged power was significantly different between background and occipital UPE signals for both Band1 and Band2.

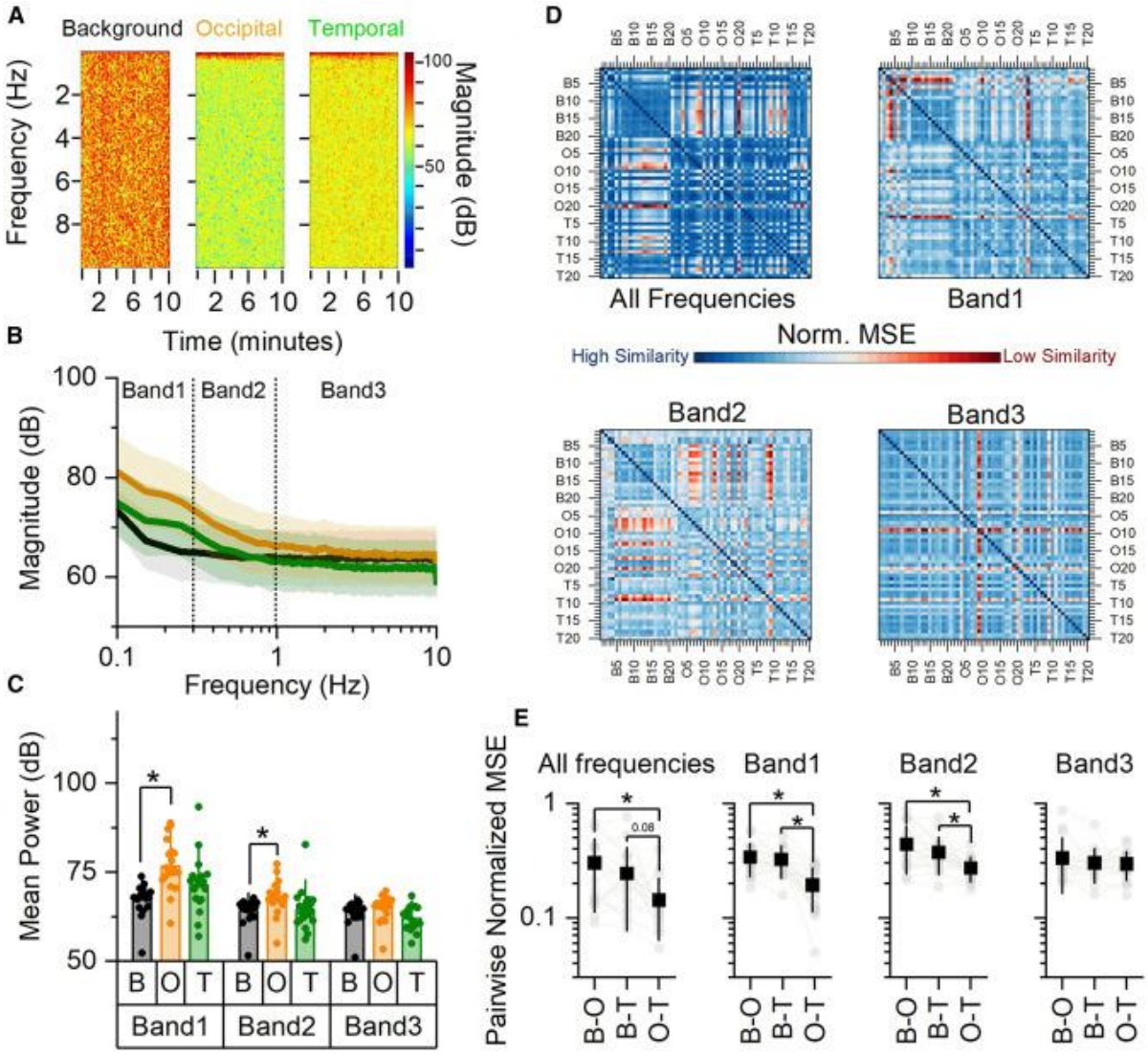

Figure 3 Brain UPE possessed unique spectral signature below 1 Hz

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Since the prior analysis averaged the UPE signals over time, we further investigated whether the inclusion of the UPE temporal dynamic confirmed a unique brain spectral pattern compared to the background. We used an imaging approach to quantify signal similarity across all pairwise combinations of UPE signal spectrograms (similarity was quantified using the MSE value; see STAR Methods). In Figure 3D, the similarity matrices for the entire UPE spectrograms and each individual band are shown. The pairwise normalized MSE values summarized in Figure 3E confirmed that the spectrograms of occipital and temporal UPE signals are more similar to each other below 1 Hz (lower MSE values; Band1 and Band2) compared to the background UPE spectrograms. While analyzing Band3, the brain UPE spectral signature was indistinguishable from background. These results showed that the brain UPE signals had a distinctive frequency signature in the range 0.1–1 Hz, implying rhythmic emission patterns or bursts ranging from once every 10 s to once every second.

Brain UPE signals exhibit discrete stationary counts changing across task

After having examined the temporal changes in UPE signals, we tested the hypothesis that different brain states are associated with defined and stable UPE counts. We proposed that, if the brain state remains stable (the same task is prolonged in time) and enough time is allowed (considering that UPE operate on slower time scales than electrical activities), UPE counts reach a stationary state. Accordingly, changes in UPE signals can only be detected during task transitions. If the hypothesis was correct, the implications included, but were not limited to, achieving a stationary signal and observing task-dependent changes in brain-derived UPE signals, as different tasks correspond to different brain states. Therefore, we tested the hypothesis that, by the end of each 2-minute-long task, a stationary UPE count is reached and that this count varies specifically between eyes open/closed tasks in the brain signals. Representative UPE trace (black) with the last 10 s (arbitrary time stretch; small enough to test robustly for stationarity and long enough to be potentially of biological relevance) for each task highlighted (blue) and magnified are shown in Figure 4A. To determine whether a stationary UPE count is reached at the end of each task, we first computed the deviation of each UPE count from its median for each 10-s segment (Deviation, Figure 4B). Segments were classified as stationary if their median deviation was lower than 0.015 (see STAR Methods), indicating that the median deviation of the UPE segment from its median value was lower than 1.5% (Figure 4B, green trace). We formulated the stringent null hypothesis that, by chance, only 5% of the segments are not stationary under the assumption of a stationary UPE count at the end of each task. We then determined the fraction of stationary vs. non-stationary segments for each PMT and compared it to null hypothesis. All PMTs showed a stationary UPE signal in the last 10 s of each task (Figure 4B).

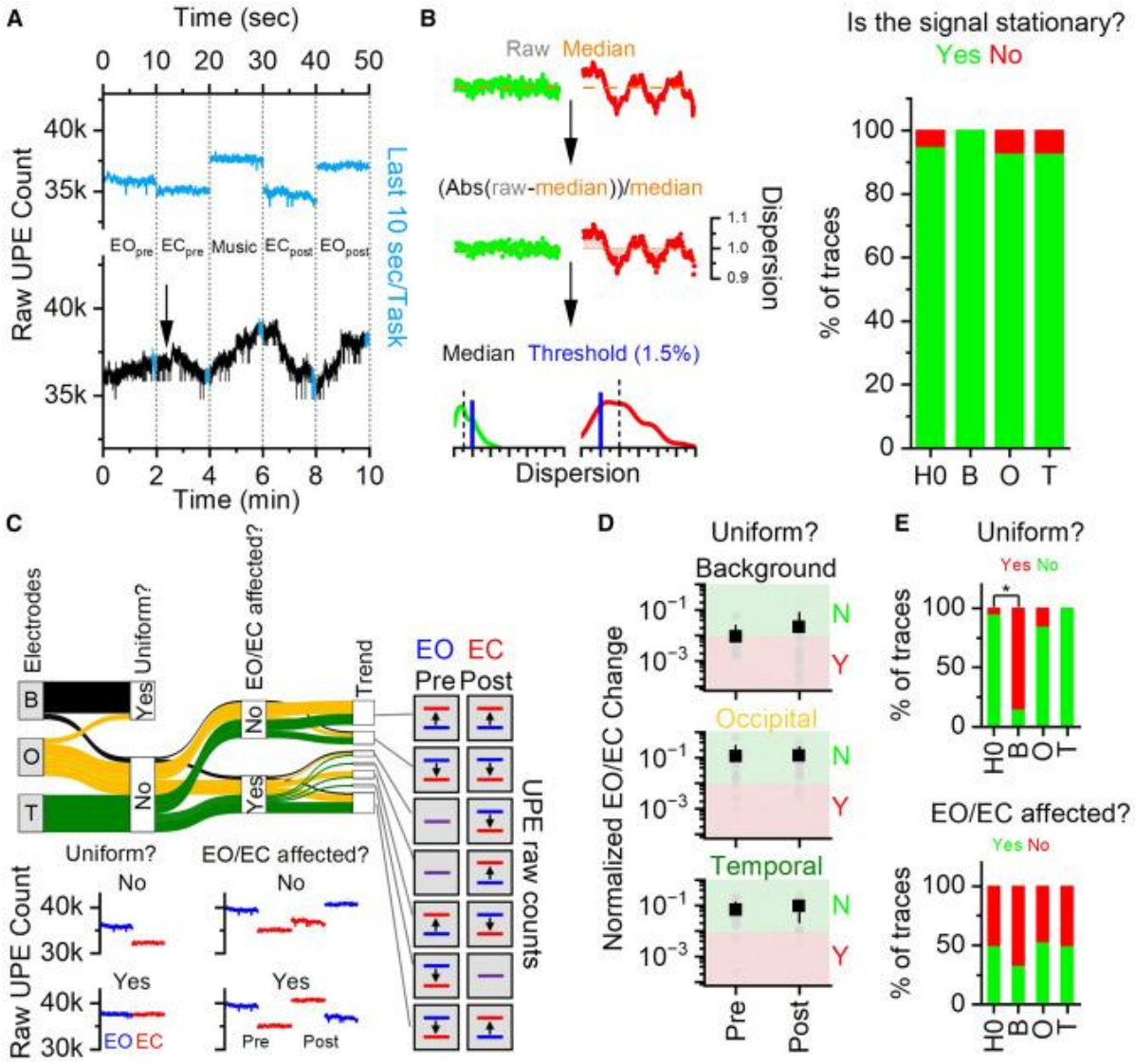

Figure 4 UPE signals reached a stationary signal at the end of each task and only the brain UPE traces showed task-to-task changes

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We then examined whether the relative UPE stationary counts varied between Eyes Open (EO) and Eyes Closed (EC) tasks, based on the hypothesis that brain UPE counts may reflect distinctions between these two brain states. While the tasks included an auditory stimulus (music), we analyzed the relative UPE count changes only across EC and EO tasks. In fact, unlike M, EC and EO tasks have well-established and robust distinct brain signatures. The alluvial plot in Figure 4C summarized the fraction and type of UPE signals that were considered uniformed or variable (Yes and No, respectively), changed the EO/EC relative count before and after Music and their specific trends. Representative traces for each condition are shown in Figure 4C. For each EO/EC pair before and after the Music task, we computed the normalized UPE change (Figure 4D; see STAR Methods). We classified a UPE signal as variable (green shaded area) if the EO/EC change either before or after Music exceeded 0.009 (three times higher than the median change in the background signal); otherwise, it was considered uniform (red

shaded area). Figure 4E (top) showed the percentage of UPE traces classified as uniform across PMTs. We formulated the stringent null hypothesis that the traces were not uniform by chance (5%), under the assumption that brain UPE counts vary between EO and EC tasks. The background condition, but not the brain signals, violated the null hypothesis.
We finally examined whether exposure to the auditory stimulus affected the relative UPE count between EO and EC tasks (Figure 4E, bottom). All conditions failed to reject the flat null hypothesis that M had an equal chance to change or not the trend. The results demonstrated that a stationary signal is achieved, and significant variations across tasks were observed exclusively in brain UPE signals. However, the direction of these changes was not consistent among subjects before and after the M task.

Brain spectral power displays condition-dependent correlations with UPE measures

Upon examination of the qEEG data (n = 20), we identified two (n = 2) participants with significant electrical artifacts within their records, thus preventing spectral power density (SPD) extractions across some tasks. Both participants were excluded from analyses involving qEEG data.
To determine whether brain rhythms associated with lobes proximal to PMTs were affected by tasks, we examined averaged SPDs ($\mu V^2\ Hz^{-1}$). As expected, alpha (7.5–14 Hz) SPDs increased over both the left and right occipital lobes (O1 and O2 sensors, respectively) when participants' eyes were closed (EC) relative to when they were open (EO) (Figure S1A). The EC condition also produced increased theta (4–7.5 Hz) SPDs and decreased beta 1 (14–20 Hz) SPDs when compared to EO. Delta and gamma rhythms were not impacted by EC-EO conditions. These results confirmed that brain rhythms were reliably affected by closing one's eyes in a relaxed state and provided context for task-dependent UPE changes reported elsewhere.
We then tested the hypothesis that occipital UPE counts and alpha-band SPDs vary systematically. Performing simple linear regression, during the EO condition, there were no discernable relationships between UPEs and SPDs. However, when the participants closed their eyes (EC condition), both background and occipital UPEs (averaged over the EC condition period) correlated with alpha-band SPDs over the occipital lobes (Figure 5A). There was no discernable relationship between temporal UPEs and alpha SPDs from the occipital regions.

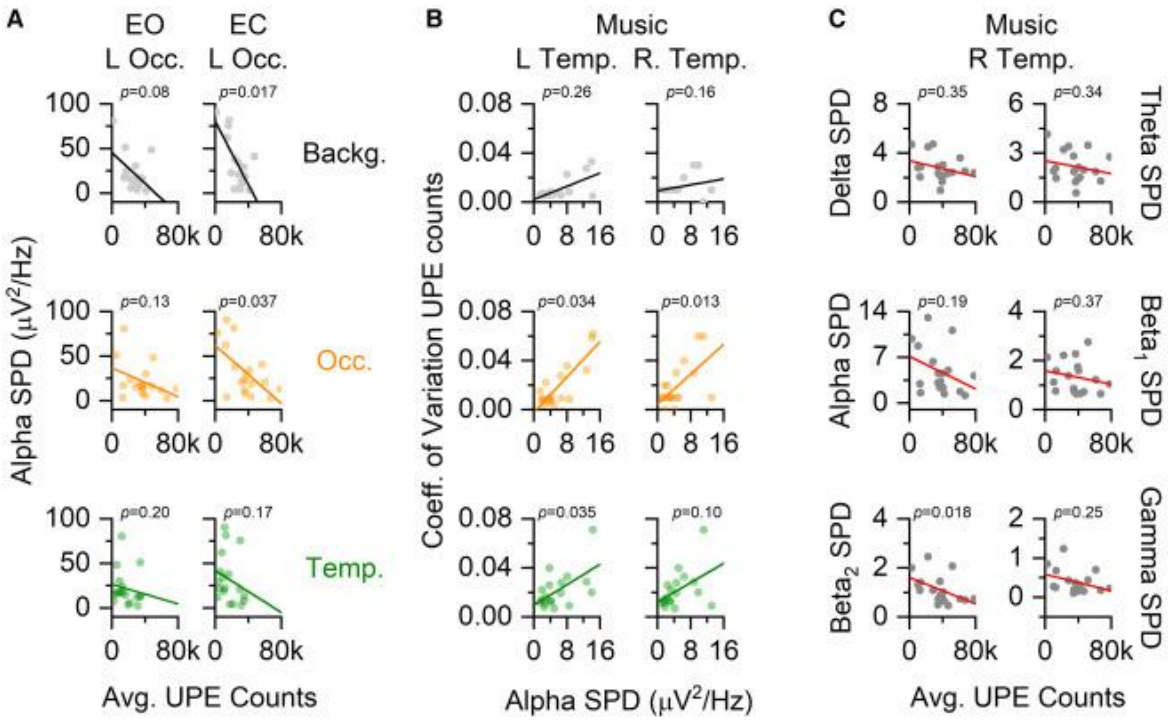

Figure 5 Brain SPDs display condition-dependent correlations with UPE measures

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Next, we sought to determine whether SPDs over the temporal lobes were affected by the 120 BPM auditory stimulus (M condition). As expected, due to the right-sided presentation of the stimulus, high-frequency activity across beta 1 (14–20 Hz), beta 2 (20–30 Hz), and gamma (30–40 Hz) spectral bands decreased significantly over the left temporal lobe (contralateral to the stimulus) during the M condition (Figure S1B). Lower frequency (1–7.5 Hz) SPDs within the left temporal lobe was not affected by exposure to an auditory stimulus. Right temporal lobe SPDs were not affected by auditory stimulation across all bands (delta-gamma). Then, we tested the hypothesis that high-frequency SPDs over the temporal lobes would correlate with average UPE counts over the same region during the M condition, though no relationship could be discerned. However, a relationship between right temporal beta 2 SPDs and occipital UPE counts was identified, which was not evident at any other frequency band (Figure 5C). There was no relationship between background photon counts and temporal lobe SPDs. Interestingly, during the M exposure, temporal and occipital UPE variability (CV) correlated with alpha SPDs over the left temporal lobe (Figure 5B). Only occipital UPE variability correlated with alpha SPDs over the right temporal lobe. Background photon variability did not correlate with any temporal lobe brain rhythms during auditory exposures.

Together, these data indicate that although UPE and SPDs may vary together during tasks that change SPDs, and relationships tend to be within expected frequency bands associated with task-dependent SPD changes, there are unexpected effects across qEEG-PMT proximal sensor pairs.

Discussion

As the first proof-of-concept demonstration that UPEs from human brains can serve as readouts to track functional states, we measured and characterized photon counts over the heads of participants while they rested or engaged in an auditory perception task. We demonstrated that brain-derived UPE signals can be distinguished from background photon measures. Additionally, our results suggest that for a given task, the UPE count may reach a stable value (steady state). The data indicated that the primary distinguishing factor between brain vs. background UPE signals was the variation in raw count of brain UPE traces across different tasks. This variation was reflected in the increased variability and information content (Figure 2). Additionally, these changes occurred at frequencies below 1 Hz (Figure 3), suggesting a different rate of change between electrical (qEEG) and UPE signals. Indeed, we predict that fast brain state shifts might not be reflected in the UPE trace dynamics. If metabolically driven UPE fluctuations and electric field oscillations operate at different scales of time, there will be a need to identify the relevant transform that enables an analysis of mutual information or shared variances.

On the basis of our initial observations, we proposed and began to explore a novel hypothesis: UPE counts are stationary for a long-enough task (Figure 4). Although this suggests a relationship between UPE counts and electrical oscillations in the brain, our current dataset only supported a limited analysis of their potential connection (n = 18). Nevertheless, we did identify correlations between UPEs and qEEG spectral power (Figure 5), motivating future investigations with higher density sensor arrays. However, future investigations should involve larger sample sizes and designs incorporating distinct tasks that generate unique qEEG profiles. With the ability to synchronize PMT and qEEG recordings at the millisecond scale, there is the potential to observe UPE dynamics during highly stereotyped event-related potentials (ERPs). However, it remains uncertain whether strong correlations between neural oscillations and UPEs should be anticipated, given their different generative mechanisms and timescales. Brain UPEs may also be differentially expressed by inhibitory or excitatory neurons as well as by glial cells, which serve complex metabolic functions. If circum-cerebral UPEs reflect the brain's regional metabolic load, they may also reflect individual differences of functional connectivity and other factors. Alternatively, a variation in the rate of change of the UPE signals could suggest that various brain regions achieve a steady state at different times.

It was originally assumed that UPE dynamics would differ as a function of whether the participants' eyes were open or closed, reflecting the well-documented effects on alpha rhythms associated with this standard neuroimaging task using electroencephalography. Given that neural oscillations within the alpha band are reliably modulated by the presence or absence of visual stimuli, we predicted that similar changes in UPEs would be detected with increased metabolic activity among active cell populations—particularly within the occipital lobe. We did observe brain UPE count differences as a function of whether participants' eyes were open or closed (Figure 4E). However, the relative change in counts between these tasks varied among subjects, possibly indicating that either the tasks alone did not fully explain the direction of UPE change or the direction of UPE change was weakly linked to the task. There may be a

temporal disconnect between UPE-generative mechanisms and those that underlie neural oscillations that could account for this unanticipated finding.

Interestingly, background photon counts and occipital alpha SPDs correlated when participants' eyes were open (Figure 5A). It may be relevant that, in previous studies, alpha rhythms over the occipital lobe were found to correlate with ambient magnetic field fluctuations in real time[43,44,45] and could be attenuated by magnetic shielding and rescued by exposures to artificially generated simulations of Earth's magnetic field.[46] We have previously highlighted that alpha rhythms may be, in part, driven by exogenous stimuli.[32] In the present study, we determined that when participants closed their eyes, background photons and UPEs over the occipital lobe varied systematically with occipital alpha rhythms. Temporal UPEs, while displaying dynamics that were similar to occipital UPEs and distinct from background photons, did not correlate with brain SPDs. Together, these data support a potential connection between brain rhythms, UPEs, and ambient electromagnetic conditions; however, further experiments with shielding conditions are needed to make conclusive statements.

As brain UPE detection technologies continue to develop, it will be important to consider several factors to optimize their predictive power. For example, UPE wavelengths were not considered in the current study but were previously found to be predictive of aging,[24,25,27,28] cognitive potential,[29] as well as essential discriminants of healthy and diseased states.[47,48] Our PMTs were calibrated to detect a wide band of UPE wavelengths, which was intentionally inclusive but may have obscured or diluted narrow-band effects. Thus, the use of filters or tunable photodetectors is recommended to determine the wavelength dependencies of brain UPE pattern signatures. Similarly, the present study involved the use of limited sensor array over a few regions of interest. To better understand how brain UPE patterns are related to connectomes and enable deep-tissue source localization, it will be necessary to use higher density arrays of photodetectors that will greatly improve the spatial resolution of the technique. Unlike electric field oscillations, which when detected by qEEG reflect nearby cell activations (likely within the first few millimeters of cerebral cortex), UPEs detected over the surface of the head could originate from many radiative point sources within the cerebrum—particularly from superficial regions where expected attenuation is not as extreme. This could explain why we observed a relationship between left occipital UPEs and high-frequency oscillations within the right temporal lobe (Figure 5C). Because UPEs are generated by molecular reactions, the number of potential point sources for emissions far exceeds the number of cells within the system. Although this may complicate source localization, we would suggest that a combination of detector arrays and machine learning tools could enable engineers to re-construct UPE dynamics in three-dimensional space for neuroimaging applications—particularly if UPE point sources are spatially clustered rather than homogenously distributed. Because UPEs are related to oxidative metabolism, the most immediately relevant applications might include the detection of budding brain tumors, excitotoxic lesions, mild traumatic injuries, and neurotoxic insults (e.g., chemobrain).

Toward engineering a "photoencephalography" technique with which to infer functional brain activations on the bases of endogenous light emissions coupled to oxidative metabolism from neural tissues, additional experiments are needed to isolate key signal parameters. One of the major challenges that must be overcome before brain UPE

measurements become a practical reality for clinical applications is the identification of fingerprint-like patterns akin to ERPs and other stereotypical features. However, just as MEG measurements reveal femtoTesla-scale (10^{-14} T) magnetic field fluctuations that are predictive of brain states despite microTesla-scale (10^{-6} T) ambient magnetic noise (100 million times more intense), we view the current results as a proof-of-concept demonstration that patterns of human-brain-derived UPE signals can be discriminated from background light signals in darkened settings despite very low relative signal intensity. Photoencephalography would be maximally non-invasive (i.e., passive recording) with high temporal resolution, like EEG or MEG; however, the measurement of UPEs would be linked to oxidative metabolism with several clinical applications described elsewhere. Future studies may find success in using select filters and amplifiers to sieve and enhance UPE signal features from healthy and diseased brains.

Limitations of the study

One limitation of the study was a lack of simultaneous non-brain tissue PMT measurements to differentiate UPE generators by metabolic load, ROS production, heat production, electrical excitability, and other physiological features. Similar to the inclusion of multiple PMTs to source-localize UPEs in the brain, additional PMTs across the body may help disentangle unanswered questions about the relationships between UPEs and systemic physiology. Future studies should incorporate measurements from limbs, digits, and other organs (e.g., liver, heart) that may display unique, tissue-dependent signal properties. If signals can be discriminated with UPE signals alone, there may be several biomedical applications that go beyond neuroimaging. Although the sample did include similar proportions of self-identified men and women, it should be noted that the small sample limited a detailed exploration of gender- or sex-based differences. Future studies should aim to identify unique UPE signatures reflective of known metabolic and neuroanatomical differences across these groups.

Resource availability

Lead contact

Further information and requests for resources, data, and codes should be directed to and will be fulfilled by the lead contact, Dr. Nirosha J. Murugan (nmurugan@wlu.ca).

Materials availability

All materials and methods are presented in the paper, are available on Zenodo (https://zenodo.org/records/13903556), or can be made available upon request from the lead contact.

Data and code availability

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Data: all data are presented in the manuscript and can be accessed upon request from the lead contact.

- Code: standard MATLAB code was used for analysis, all of which can be found explicitly named under the quantification and statistical analysis section. For each panel, the model, dataset, and modeling parameters are available on Zenodo (https://zenodo.org/records/13903556).
- Additional information: any additional information that is required to analyze the data reported in the paper can be obtained by contacting the lead contact.

Acknowledgments

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Author contributions

Study conception and design, N.M. and N.R.; data collection, H.C. and I.D.; data processing and management, H.C., I.D., and M.B.; analysis and interpretation of results, N.M., M.B., and N.R.; draft manuscript preparation, N.M., M.B., and N.R.; revisions, N.M., N.R., and M.B. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

The authors report no conflicts of interest, financial or otherwise.

STAR★Methods

Key resources table

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
MATLAB	MathWorks, Inc.	Version 2023b
Standardard MATLAB Code	Zonodo (archived)	https://zenodo.org/records/13903556 https://doi.org/10.5281/zenodo.13903556
Windows 10 OS	Microsoft	20H2
Counter Timer Software	Sens-Tech	Version 2.8, Build: 11

REAGENT or RESOURCE	SOURCE	IDENTIFIER
WinEEG Software for Mitsar	Bio-Medical, Inc.	#NTE WINEEGADV
Other		
Mitsar-202 QEEG amplifier	Bio-Medical, Inc.	#NTE MITSAR20224
19-Channel Electro-Caps	Bio-Medical, Inc.	#ECA CAPS
Electro-gel for Electro-Caps	Bio-Medical, Inc.	#ECA E9
BD Luer-Lok Tip Syringes - 5mL	Bio-Medical, Inc.	#ECA E7B-5ML
Electro-Cap Tin Ear Electrodes - 9mm	Bio-Medical, Inc.	#ECA E5-9S
Photomultiplier Tubes	Sens-Tech	DM0090C
Gooseneck Mount/Clamp	Lamicall	LS05-CA-B
Smartphone	Google	Pixel 7 (GVU6C, GQML3)
Laptop Computer	DELL	Inspiron 15 (7000)

Experimental model and study participant details

Participants

A total of twenty (n=20) adults were recruited with publicly displayed advertisement and consented to the participate in the study. The sample consisted of 10 women, 9 men, and 1 non-binary individual, with a mean age of 25.4 years (range: 19–52) (see Table S3 for demographics details). All participants were naïve to the purpose of the experiment and were asked to follow basic instructions while sitting in a darkened room. All participants had normal or corrected-to-normal vision and reported no history of mental health problems or neurological disorders. Participants were not allocated to specific groups because of the within-subject experimental design (i.e., all participants receive the same exposure conditions). Written informed consent was obtained from all of the participants. All study procedures were conducted after approval from the institutional Research Ethics Board at Algoma University (Study Approval Number: 026-202122).

Method details

Measurement chamber

The study involved the simultaneous measurement of scalp surface potentials and UPEs over the participant's head during a 10-min recording period. Before initiating the recordings, participants were guided to a darkened room, which comprised of a small chamber (2.2 m x 1.5 m) within a larger darkened laboratory space and sat in a comfortable, padded chair. qEEG and PMT devices were positioned on or around the head as described elsewhere. The enclosed chamber was darkened with black wall coverings and the external laboratory space was devoid of all light sources with the exception of laptops used for qEEG and PMT recordings, which were set to minimum

brightness settings. Cables connecting computers in the outer laboratory space and sensors in the chamber passed through small holes located at the bottom of the chamber wall behind the participants.

General procedure

Following a brief description of the procedures, darkening the room, and uncovering PMTs, the recording were initiated and carried out in the following order: (1) 2 mins of baseline recordings with the participants' eyes open (EO-Pre), (2) 2 mins of baseline recordings with the participants' eyes closed (EC-Pre), (3) 2 mins continuous exposure to an auditory stimulus (M), (4) 2 mins of baseline recordings with participants' eyes closed (EC-Post), (5) 2 mins of baseline recordings with participants' eyes open (EO-Post). After the recording procedure, PMTs were covered, lights were turned on, the EEG cap was removed, and the participant was debriefed. Data were always collected during the daytime, between 9:00 and 18:00 EST.

Auditory stimulus

An auditory stimulus consisting of a repeating (120 bpm, 2 Hz) click with a woody "block" timbre and spectral peak of 921 Hz was delivered via a Google Pixel 7 smartphone, placed outside of the darkened chamber. The stimulus was always delivered without warning to the right side of the body at the 4-min time point of the experimental procedure when participants' eyes were closed, and individuals were later asked to confirm the audible sounds after the full, 10-min recording period. For the purposes of labelling only, conditions involving the auditory stimulus will be referred to as "music" or "M" throughout the analysis. Similar auditory stimuli were previously found to affect high-frequency brain rhythms.[49,50]

Ultraweak photon emissions (UPEs)

Photomultiplier tubes (PMTs) (Sens-Tech DM0090C) were positioned around the participants to record photon counts (s-1) indicative of ultraweak photon emissions (UPEs). Each device contained a 22-mm S20 cathode, displayed a spectral range of 300-850 nm, and was rated for typical dark counts of ~1000s-1. Devices logged data via a USB connections to DELL laptops running Windows 10 OS and powered by an external 9V AC supply (input voltage was ~5V).
Two PMTs were positioned approximately 5 cm over the surface of the head with their apertures facing corresponding brain regions of interest, including the left occipital lobe (PMT-O) and right temporal lobe (PMT-T). The PMT-O aperture was always facing the head and positioned medial to the O1 sensor of the qEEG cap, while the PMT-T aperture was always positioned slightly ventral relative to the T4 sensor of the qEEG cap (19-channel ECI Electro-Cap). A third PMT was placed approximately 30 cm anterior and 10 cm lateral to the participant on their left side, with its aperture pointed toward a wall, away from the door. Standard measurement parameters were set within the Sens-Tech Counter Timer Software, including high-cut (30 Hz), notch-filter (60-120 Hz), and gain (100 μV). The period of recording was set to 40 ms (25 Hz) for a total

of 15,000 measurements within 10 minutes. Devices were only uncovered while in darkened environments, with a 5-min buffer between exposing apertures and initiating recordings.

Quantitative electroencephalography (qEEG)

Microvolt (μV) fluctuations over the surface of the scalp were measured with a quantitative electroencephalography (qEEG) system (Mitsar-202 amplifier) connected to a DELL laptop running WinEEG software on a Windows 11 OS. Each participant wore a 19-channel cap with sensors distributed according to the 10-20 international system (19-channel ECI Electro-Caps). A monopolar montage was used, referenced to two electrodes attached to participants' ears. Impedance values of less than 5 kOhm were always achieved before initiating recordings. Measurements were collected at a sample rate of 250 Hz, with 100 μV gain and applied low-cut and high-cut filters of 1.6 Hz and 50 Hz, respectively. Notch-filters of 50-70 Hz and 110-130 Hz were also applied. Spectral densities (μV2 Hz-1 or SPDs) were extracted from WinEEG from 30 second segments of raw data, yielding 4 extracts per 2-minute condition. Default band ranges were defined as the following in WinEEG: delta (1.5Hz-4Hz), theta (4Hz-7.5Hz), alpha (7.5Hz-14Hz), beta1 (14Hz-20Hz), beta2 (20Hz-30Hz), and gamma (30Hz-40Hz). Before analysis was performed, several averaged variables were computed, including averaged SPDs over the full task period, and lobe- and/or hemisphere-specific aggregates (e.g., right temporal lobe: SPD averages of T4 and T6 sensors).

Quantification and statistical analysis

Hierarchical clustering analysis

Raw UPE count signals had been used as input of the *clustergram.mat* function, using *correlation* as a distance metrics (to compare patterns rather than absolute values) and *average* as linkage method (balanced approach less sensitive to outliers). Pairwise distances have been extracted after computing the distance matrix using *pdist.mat* function followed by *squareform.mat* function.

Entropy and coefficient of variation

Shannon's entropy of UPE signals have been computed accordingly to:

$$H(X) = -\sum_{x \in X} p(x) \cdot \log 2 p(x)$$

where $H(X)$ is the entropy of the variable X, $p(x)$ is the probability of the xth event occurring, $p(x) \cdot \log 2 p(x)$ represents the information content of the xth event weighted by its probability. $p(x)$ has been computed dividing the vector of the *histcounts.mat* function by its sum, using either the entire trace or each task as input. The number of bins for the *histcounts.mat* function has been selected by using the Freedman-Diaconis rule, ensuring that the histogram provided an informative representation of the data's distribution. Briefly:

$$bin\,s = range\,bin\,width = celi(\max(x) - \min(x)) \cdot 3\sqrt{n}2 \cdot IQR$$

where (max(x)−min(x) is the range of the distribution, n is the total number of points in the distribution, IQR is the interquartile range. The optimal number of bins has been selected as the median bin numbers across all traces and PMTs, resulting in 49 and 35 bins for the entire trace or for each two-minutes-long task, respectively. Coefficient of variation (CV) has been computed as the ratio between the standard deviation and the average of the entire trace or within task.

Short-time Fourier transform

The short-time Fourier transform (STFT) has been used to analyze the frequency content of nonstationary UPE signals over time. *stft.mat* function has been used with a time window of 20 seconds and a fraction of overlap between two consecutive windows of 75%; the spectral leakage has been reduced using Hanning window. The spectrogram has been reconstructing by plotting the power (in dB) over time at each frequency. Considering the frequency of acquisition of UPE signals of 20 Hz and the time window of 20 seconds, the frequency range was analyzed between 0.1 Hz (twice the smallest analyzable frequency of 0.05 Hz) and 10Hz (half the frequency of acquisition).
For each frequency band (Band1: 0.1-0.3 Hz; Band2: 0.3-1 Hz; Band 3: >1 Hz), mean power has been computed across the entire trace within the frequency band range.
To quantify and compare the similarity of the spectrograms, hence considering their temporal dynamic, we applied the *immse.mat* function, a metric to quantify the pixel-by-pixel similarity between two images (spectrograms). Briefly, the mean-squared error (MSE) is computed for each pairwise combination of spectrograms, whether lower values indicate greater similarities. The resulting similarity square matrix was then used to perform a hierarchical clustering analysis. We performed the analysis of the entire spectrogram, of the spectrogram with frequencies lower than 1 Hz (due to the low number of points in Band1 and the inability to perform the *immse.mat* function, the Band1 and Band2 were merged) or grater than 1 Hz (Band3).

Signal stationarity

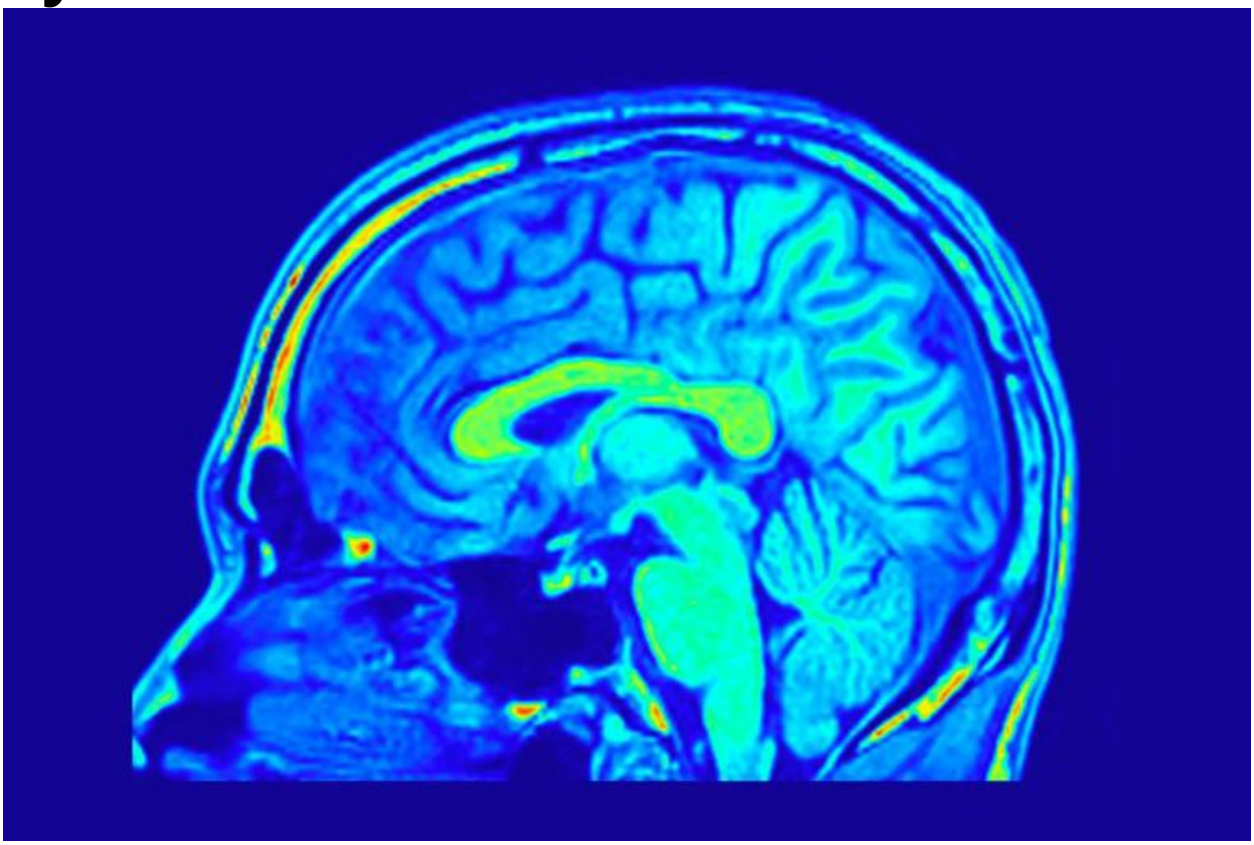
After extracting the last ten seconds of UPE raw counts for each task across PMTs, each trace has been filtered by calculating the moving average
using *movmean.mat* function, with a window of 10 points (500ms). Subsequently, we calculated the median value for each filtered segment and used it to determine the deviation, defined as the absolute difference between the filtered segment and its median, divided by the median itself. The median of the resulting deviation values was then compared to an arbitrary threshold of 0.015. This threshold corresponds to a median deviation of 1.5% from the median value of the trace. If the median of the dispersion values was less than 0.015, the segment was classified as stationary; otherwise, it was considered non-stationary.
To determine if the stationary signal varied between eyes closed/open tasks, we computed the averaged values of the last ten seconds for each task and normalized by the average UPE count of the first task (Eyes Open, Pre Music) within subject. Based on median change (computed as the absolute difference between eyes open *vs* closed

task before and after music) of 0.003 in the background signal (under the assumption that the background UPE should not vary in a task-dependent manner), we classified the UPE stationary signal as variable if the change either before or after music was greater than 0.009 (three times greater than the median change in the background signal); otherwise, it was considered uniform.

Statistical syntax

Unless otherwise indicated, statistical analysis has been conducted using generalized linear mixed-effect models (glme) in MATLAB, particularly to account for the nested structure and repetitive nature of the experimental design. For each model, the distribution (Normal, Gamma, Inverse Gaussian) and fit method (REMPL, MPL) have been selected by choosing the model maximizing the relative likelihood (i.e., $\mathcal{L}T=e0.5\cdot(AICmin-AICi)$, where $AICmin$ is the minimum AIC across all models and $AICi$ is the AIC for the ith model) and visual analysis of the residual. Chi-square proportional test results have been calculated after creating a contingency table and using it as an input for the *crosstab.mat* function. *Post-hoc* analysis has been performed using Bonferroni's correction with alpha=0.05. For paired samples, the effect size has been computed as $d=DsD$, where D is the averaged difference between paired samples ($D=\sum ni=1(xn-yn)n$, where n is the number of paired measures, x is group 1 and y is group 2) and sD is the standard deviation of D. For each panel, the dependent and independent variables, and statistical details (F-Statistic, degrees of freedom, p-values) have been summarized in Table S1.

Brain Network That Supports Logic, Reason, And Problem-Solving Pinpointed by New Tests



Two new tests have been developed by working with patients with advanced lesions on their brains. - Image credit: FocalFinder/Shutterstock.com© IFL Science

Researchers have identified the brain regions that are essential for logical thinking and problem-solving. The findings help us understand how our brains support our reasoning skills – our ability to comprehend, draw conclusions, and deal with novel problems.

Reasoning skills are pretty important. They underpin many of humanity's greatest intellectual achievements – from mathematics, philosophy, and science, to pub quizzes, internet memes, and overly competitive games of *Scrabble*. Given its significance in human affairs, reason itself has been the subject of centuries of academic interest, but our understanding of the relationship between reasoning abilities and other cognitive processes, as well as their neuroanatomical basis, is still quite limited.

To assess which brain areas are necessary for certain abilities, researchers study patients with brain lesions – damaged areas – caused by stroke or brain tumors. This approach is known as "lesion-deficit mapping". It's probably the most powerful way we have to localize functions in the human brain. However, it is not easy to perform.

Studying brain injuries is complex and time-consuming, as researchers need a large number of patients with specific brain damage. For instance, they may be looking for patients who have difficulty thinking, feeling, or moving, but few research centers have access to sufficient patients with the same problems to conduct this kind of study effectively.

Previous research has tended to rely on functional magnetic resonance imaging (fMRI) techniques in healthy individuals, where brain activity is detected by imaging changes in the blood flow and oxygenation in the brain. However, the results this technique offers can sometimes be misleading, as it provides correlational evidence, not causal.

In their latest study, a team led by researchers at UCL Queen Square Institute of Neurology and Department of Neuropsychology at the National Hospital for Neurology and Neurosurgery, UCLH, used lesion-deficit mapping to examine 247 patients with unilateral focal brain lesions in either the left or right frontal or posterior regions of the brain. In addition, 81 healthy individuals were included to serve as a control group.

Two tests were used to assess reasoning skills in these participants. These included a verbal deductive reasoning task – a puzzle where participants are asked to find relationships between words to solve and problems. This included questions such as "*If Sarah is smarter than Diana and Sarah is smarter than Heather, is Diana smarter than Heather?*"

The second test was a nonverbal analogical reasoning task – a type of puzzle involving pictures, shapes and numbers that are used to solve problems or identify patterns. They were asked questions like "*Which set of numbers is 1,2,3 most similar to – 5,6,7 or 6,5,7?*".

The results shows that people with damage to the right frontal lobe found it much harder to complete both tasks compared to those with damage to other areas. They made about 15 percent more mistakes than the other participants.

“Our study explores how the front right part of the brain helps people think and solve new problems,” lead author Dr Joseph Mole explained in a statement.

“It also shows that our two new tests can help detect reasoning problems in individuals with brain damage, improving diagnosis and treatment.”

“By combining a detailed cognitive investigation in a large sample of brain damaged patients with advanced lesion mapping techniques – developed by Professor Parashkev Nachev and his team at the UCL Queen Square Institute of Neurology – we have deepened our understanding of the complex and, so far, poorly understood, neural structures underlying human reasoning,” Professor Lisa Cipolotti added.

“Our findings show a close connection between the right frontal brain network involved in reasoning and the right frontal brain network essential for fluid intelligence (our ability to solve problems without prior experience). This suggests that a common area of the brain plays a critical role in both reasoning and fluid intelligence.”

The team believe these findings have important clinical implications, as the tests can help identify cognitive impairment that would usually go undetected. They hope that, with further validation and implementation, the new reasoning tests could be rolled out on the UK's National Health Service, offering tools specifically designed to assess right frontal lobe dysfunction.

The study is published in the journal Brain.

A right frontal network for analogical and deductive reasoning

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Abstract

Two of the most well-studied types of reasoning are analogical reasoning (AR) and deductive reasoning (DR). Yet, our understanding of the relationship between reasoning abilities and their neuroanatomical basis remains surprisingly limited. We aimed to conduct fine-grained anatomical mapping of performance on tests of AR, DR and fluid intelligence (Gf), in a large sample of patients with unilateral focal frontal or posterior lesions and healthy controls.

We assessed 247 prospectively recruited patients using two new tests: the Analogical Reasoning Test (ART) and the Deductive Reasoning Test (DRT); and the best-established measure of Gf: Raven's Advanced Progressive Matrices (RAPM). Non-parametric Bayesian stochastic block modelling was used to reveal the community structure of lesion deficit networks, disentangling functional from confounding pathological distributed effects.

ART and DRT performance was significantly impaired in patients with frontal lesions [ART: $F(2,238) = 18.93$; $P < 0.001$; Frontal group worse than Posterior group and healthy controls, both $P < 0.001$; DRT: $F(2,387) = 18.491$; $P < 0.001$; Frontal group worse than healthy controls, $P < 0.01$]. Right frontal effects were evident on both tests. Thus, on the ART, right frontal patients were more impaired than left ($P < 0.05$). On the DRT, right frontal patients were more impaired than left frontal patients on questions with indeterminate solutions ($P < 0.05$) but not on questions with determinate ones. Non-parametric Bayesian stochastic block modelling implicated a right frontal network in ART and DRT performance. Strikingly, we found that this network was also implicated in performance on RAPM.

Our study represents the most robust investigation of AR and DR in the focally injured brain. Our findings imply that a right frontal network is critical. The ART and DRT appear to be promising new clinical tests, capable of evaluating reasoning abilities and identifying right frontal lobe dysfunction.

Introduction

Reasoning skills are central to many of humanity's greatest intellectual endeavours: mathematics, philosophy and science, to name but a few.[1] Unsurprisingly, reasoning has itself been the subject of intense academic interest since the dawn of scientific enquiry.[2]

Two of the most well-studied types of reasoning are analogical reasoning (AR) and deductive reasoning (DR). Analogical reasoning is the process of identifying similarities between relationships (e.g. '1,2,3' is most similar to '5,6,7' or '6,5,7'?).[3] This form of reasoning is held to underpin our ability to solve problems by transferring information from one set of relationships to another. In contrast, DR is the ability to derive a logical conclusion from a set of premises that are held to be true. This form of reasoning is thought to be critical for solving problems with determinate solutions (e.g. 'If Mary is braver than John and John is braver than Michael is Mary braver than Michael?'), as well as identifying when solutions cannot be determined (e.g. 'If Sarah is smarter than Diane and Sarah is smarter than Heather is Diane smarter than Heather?').[4]

Our understanding of the relationship between reasoning abilities and other cognitive processes, and their neuroanatomical basis, remains surprisingly limited.[5] Several influential theories have proposed close links between reasoning abilities and fluid intelligence (Gf). Gf is the ability to solve challenging novel problems when prior learning or accumulated experience are of limited use.[6] The influential Cattell–Horn–Carroll theory proposes that reasoning skills are the hallmark of Gf.[6] Within this theory, Gf is considered to be a 'broad' cognitive domain comprising several qualitatively different reasoning abilities,

such as: inductive reasoning—encompassing AR, sequential reasoning—encompassing DR and quantitative reasoning—encompassing the ability to reason using mathematical concepts.

Duncan *et al*. proposed that reasoning abilities and Gf are underpinned by a network of mainly bilateral frontal and parietal areas, termed the 'multiple-demand network' (MD).[7] This proposal was largely based on functional magnetic resonance imaging (fMRI) studies in healthy adults reporting MD activation during performance on tests of reasoning, Gf and executive functioning.[7] According to this proposal, the function of the MD is best conceptualized as a single cognitive process, namely Gf. Similarly, the parieto-frontal integration theory (P-FIT) proposed that a rather large network of bilateral parieto-frontal brain areas, as well as temporal and occipital cortex, underpins performance on tests of reasoning, Gf, general and crystallized intelligence.[8]

Reasoning skills and Gf have also been thought as key mental processes involved in 'active thinking', the cognitive processes necessary for confronting situations where we do not respond routinely but, rather, effectively address novel problems.[9] Active thinking also encompasses a variety of other executive abilities, such as those involved in abstraction, switching lines of thought and formulating strategies. The general theoretical position is that different types of active thinking processes are supported by a set of potentially separable cognitive processes, underpinned by separate lateralized frontal lobe networks. In line with this, we recently reported that a rather localized right frontal network underpins performance on one of the most well-established measures of Gf [Raven's Advanced Progressive Matrices (RAPM)].[10] We hypothesized that this network may be critical to the ability to make high-level inferences based on the perception of the progression of a pattern. In contrast, we have reported preliminary findings suggesting that a left frontal network may support 'task setting': the ability to formulate a mental programme to guide action, which is needed, among other processes, when solving multi-stage calculations.[11]

Most existing studies that have investigated the anatomical substrates of AR and DR have used fMRI in healthy adults and reported rather mixed results. Several fMRI studies of AR have reported activation in the left rostrolateral prefrontal cortex[12,13] However, others have reported bilateral, or even right, frontal activation.[14-19] The results from neuroimaging investigations of DR have implicated various frontal and posterior areas, in both hemispheres.[20-23] However, it remains unclear whether these conflicting results can be accounted for by methodological inconsistencies and/or the inherently correlative nature of fMRI evidence or, instead, may hint at the existence of specialized networks supporting different aspects of reasoning.

Some authors have suggested that brain areas in both hemispheres may be critical for different types of reasoning. For example, Goel *et al*.[4] proposed that the left frontal lobe supports reasoning in situations where a solution can be determined. Instead, the right frontal lobe supports reasoning in situations where a solution is indeterminate. Prado *et al*.[24] argued that the left inferior frontal gyrus and basal ganglia underpin performance on categorical DR questions (e.g. 'All As are Bs. All Bs are Cs. Therefore, all As are Cs'), the left precentral gyrus support performance on propositional DR questions ('If there is an A, then there is a B. There is an A. Therefore, there is a B'), whereas the right middle frontal gyrus and posterior parietal cortex support performance on relational DR questions (e.g. 'A is to the left of B. B is to the left of C. Therefore, A is to the left of C'). Other authors have placed greater emphasis on the left hemisphere. For example, Holyoak and Monti[25] suggested that reasoning abilities are reliant upon several different cognitive processes involved in the representation and integration of relationships, and each process is supported by different brain areas localized in a predominantly left-lateralized frontoparietal network. Wang *et al*.[26] suggested that DR may be supported by a distributed network, encompassing left frontal/parietal cortices and subcortical structures, and a 'core' network, comprising the left inferior frontal gyrus, insula and cingulate. Reverberi *et al*.[27] argued that left ventrolateral frontal, left inferior lateral frontal and superior medial frontal cortices are critical for syllogistic

deductions, but that the pattern of activation depends upon the behavioural strategies employed. Thus, while several proposals may account for the apparently conflicting results from neuroimaging studies, it remains unclear which brain areas are critical.

An important caveat of fMRI techniques is that they cannot reliably differentiate regions activated in the exercise of a cognitive ability from those necessary for it.[28] For example, an observation of activation in a given brain area during performance on a cognitive test—even if reliably replicated over multiple studies—does not necessarily imply that this area has a direct bearing on performance.[29]

To overcome the limitations of neuroimaging methods, several authors have investigated reasoning abilities using transcranial magnetic stimulation (TMS). For example, Boroojerdi *et al*.[30] reported that repetitive TMS (rTMS) over the left frontal lobe was associated with faster response times on a test of AR, without reducing accuracy. Tsujii *et al*.[31] reported that bilateral superior parietal lobule stimulation disrupted performance on abstract and incongruent categorical DR questions, left inferior frontal gyrus stimulation disrupted performance on congruent categorical DR questions and right inferior frontal gyrus stimulation disrupted performance on incongruent DR questions. However, methodological issues complicate the interpretation of these findings. For example, it is now understood that TMS has limited coverage and its effects are not necessarily focal.[32] Furthermore, it is technically difficult to disrupt spatially extended locations simultaneously with TMS, rendering networked neural substrates hard to delineate with confidence.

Lesion studies on patients with focal, unilateral, brain damage, caused by pathologies such as brain tumour or stroke, offer a unique opportunity to further our understanding of the neurocognitive architecture underpinning reasoning.[9] In contrast to studies using functional neuroimaging, focal lesion studies provide causal—rather than correlational—evidence.[33] In comparison

with studies using TMS, focal lesion studies offer full brain coverage and an opportunity to investigate spatially extended effects. Yet, such studies are surprisingly rare. Moreover, existing studies have investigated very small patient samples, hence they are likely to be biased and have random variation. Indeed, they have reported different findings. Thus, to the best of our knowledge, only three lesion studies have investigated AR. Langdon and Warrington[34] found no significant difference on verbal and spatial AR tests between patients with unilateral anterior (left *n* = 14; right *n* = 12) or posterior (left *n* = 24; right *n* = 26) lesions. Notably, the anterior lesions extended into posterior areas, limiting interpretation of results. Schmidt *et al*.[35] investigated performance on a verbal AR task in 34 stroke patients with unilateral left (*n* = 17) or right (*n* = 17) hemisphere lesions. Only 16 patients' lesions involved the frontal lobes. Voxel-based lesion-symptom mapping (VLSM) revealed that several frontal and temporal areas were critical for performance. Urbanski *et al*.[36] reported that 27 patients with frontal lesions (left *n* = 14; right *n* = 9; bilateral *n* = 4) were less accurate than healthy controls (HCs) on a test of AR. VLSM and tractography analyses revealed that AR was impaired following damage to the left rostrolateral prefrontal cortex and some of its long-range connections. Crucially, however, in the studies of both Schmidt *et al*.[35] and Urbanski *et al*.,[36] several frontal areas were not lesioned in a sufficient number of patients to be analysed using VLSM. This, and the now well-established flaws of mass univariate lesion-deficit mapping, especially with data of this minimal scale, prevent strong inferences from being drawn about the neuroanatomical basis of AR.[37,38]

To the best of our knowledge, only two focal lesion studies have investigated DR. Reverberi *et al*.[39] reported that patients with left lateral (*n* = 10) and superior medial frontal (*n* = 18), but not right frontal (*n* = 8), lesions were significantly less accurate than HCs at solving DR questions. Notably, all DR questions included in this study had determinate solutions. Goel *et al*.[4] reported that left frontal patients (*n* = 9) were significantly less accurate at solving relational DR questions with determinate solutions, when compared with right frontal patients (*n* = 9) and HCs (*n* = 22). In contrast, right frontal patients were significantly less

accurate at solving DR questions with indeterminate solutions, when compared with left frontal patients and HCs. The authors argued that these results support the proposal that the left and right frontal lobes underpin determinate and indeterminate DR, respectively. However, a significant limitation of this study is that over two-thirds of the patients suffered from penetrating head injuries, which frequently lead to diffuse axonal injury, typically undetected by conventional neuroimaging measures.[40] Hence, these lateralized effects must be treated with caution.

Here, we conduct fine-grained anatomical mapping of performance on tests of both AR and DR, in a large sample of 247 patients with unilateral focal frontal or posterior lesions. We designed two new computerized tests: the AR Test (ART) and DR Test (DRT). Given the putatively distributed nature of the target neural substrate, we employed graph lesion-deficit mapping, founded on non-parametric Bayesian stochastic block modelling, allowing us to infer its network organization.[10] This approach has the power to disentangle distributed patterns of neural dependence from complex anatomical patterns of pathological damage itself, providing a rigorous test of network-framed hypotheses.

Materials and methods

Participants

Two-hundred and forty-seven patients with unilateral, focal lesions were prospectively recruited from the National Hospital for Neurology and Neurosurgery (NHNN; see Supplementary material for inclusion criteria). Of these 247 patients, 176 had lesions that fell within frontal (n = 102; left frontal 47; right frontal 55) or posterior (n = 74; left posterior 32; right posterior 42) areas (i.e. ≥70% of the total lesion, calculated following segmentation of MRI or CT scans (see Supplementary material).[41] There was no significant difference between tumour and stroke patients for mean time between injury and neuropsychological assessment (P = 0.30). Handedness was recorded in 239 of

the 247 patients; of these, 232 (97.1%) were right-handed and 7 (2.9%) were left-handed.

Eighty-one HCs, with no neurological or psychiatric history, were recruited to match patients as closely as possible for age, gender, years of education and National Adult Reading Test (NART) scores.[42] The study was approved by The NHNN and Institute of Neurology Joint Research Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Behavioural investigations

Participants were assessed with tests administered and scored in the published standard manner.

Background tests

Premorbid optimal level of functioning was assessed using the NART, perception using Incomplete Letters, naming using the Graded Naming Test (GNT),[43] receptive language using the last 12 items from the Test for Reception of Grammar (TROG)[44] and Gf assessed using RAPM.[45] Two widely used executive tests, known to require processes distinct from Gf were administered:[46,47] the Phonemic fluency test (total number of 'S' words generated, excluding errors)[46] and the Stroop test (total number of ink colours correctly named in 2 min, or pro-rated if completed within 2 min).[47]

Novel behavioural tasks

The ART and DRT ran on 10.5-inch iPad Pro tablet computers, using script-based psychometric software (https://www.neurobs.com/).

Analogical reasoning task

Participants were administered the ART and a Perceptual Matching Baseline Task (see Fig. 1). Both used the same type of stimuli and design, and were

inspired by tasks developed by Urbanski *et al*.36 (see Supplementary material for a detailed description of the tasks).

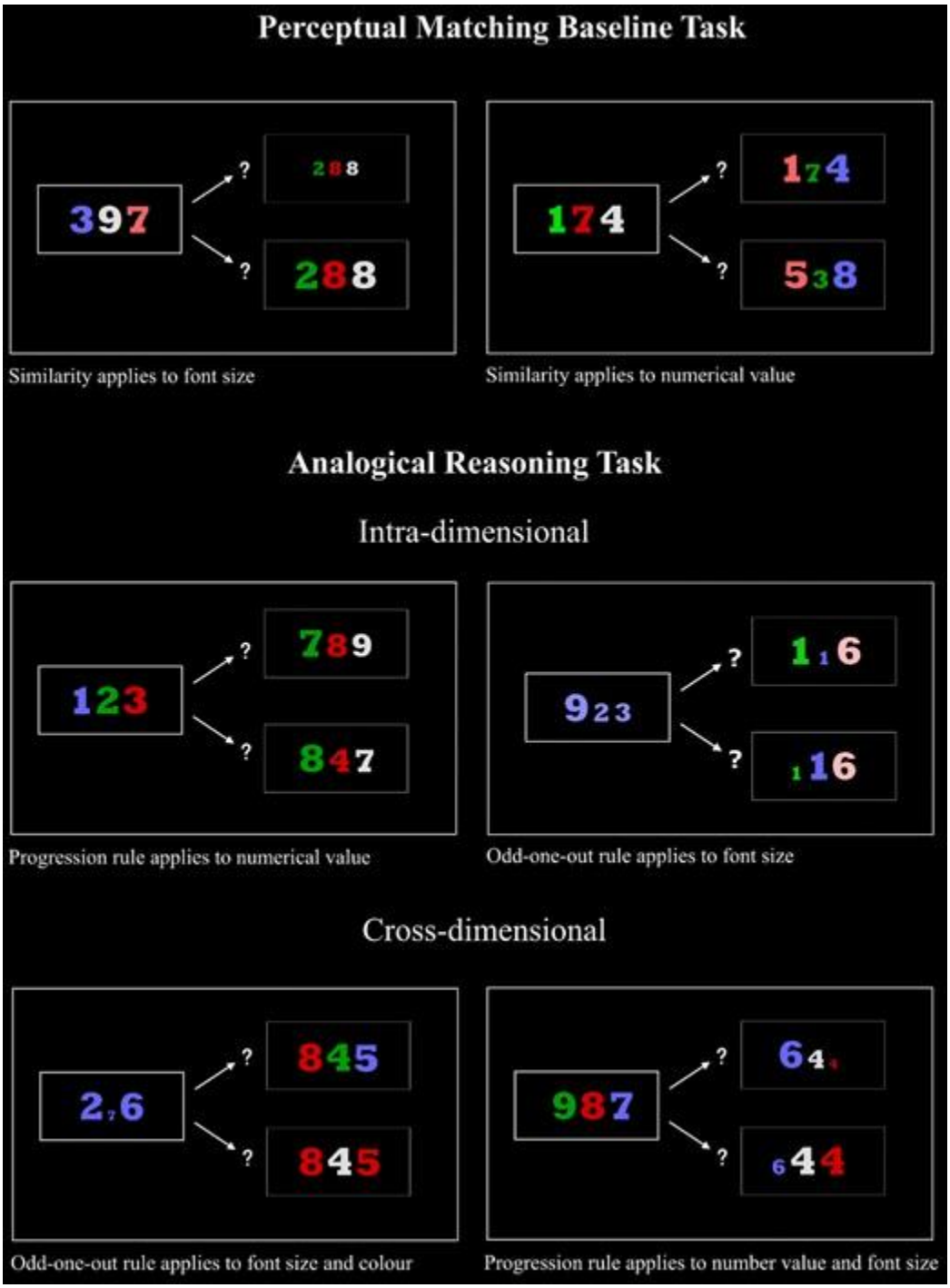

Figure 1

Example of questions from the analogical reasoning task.

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The Perceptual Matching Baseline Task began with three instruction questions, followed by 12 test questions. For each question, three sets of coloured numbers appeared on the left (the source set) and two sets appeared on the right (the target sets). Participants were told to touch the set of numbers on the right that looked most similar to the set on the left. Participants were then administered 12 test questions and instructed to respond quickly and accurately.

The ART was administered immediately afterwards. This began with six instruction questions, demonstrating the correct answers. Participants were told to again indicate which of the sets of numbers on the right is most alike the set on the left. However, this time they should do this based on whether they follow the same abstract rule.

Analogies were based on two rules: 'Progression' and 'Odd-one-out' (OOU). On Progression questions, the source and correct target set were similar because there was an increase or decrease in numerical value, intensity of colour or size. On OOU questions, the source and correct target set were similar because one of the numbers was the OOU in terms of numerical value, colour or size.

Half of the questions were 'intra-dimensional'—the analogy rule applies to the same stimuli feature (e.g. colour) in the source and target set—and half were 'cross-dimensional'—the rule applies to different stimuli features (e.g. colour and size).[36]

Following the instruction questions, participants were administered 24 test questions. They were instructed to respond quickly and accurately and feedback was provided.

We analysed the percentage of correct responses (i.e. the number of correct responses/total number of questions × 100) on the Perceptual Matching Baseline Task and ART. Percentage of correct responses was also calculated separately for Progression (n = 12), OOU (n = 12), intra-dimensional (n = 12) and cross-dimensional questions (n = 12).

Deductive reasoning task

The DRT comprised a series of 24 relational deductive reasoning questions (see Supplementary material for a detailed description). Participants were told that their task was to determine if the third sentence follows logically from the first two sentences, by pressing either 'Yes' or 'No'.

Participants were presented with two practice questions. The first was determinate and logically valid (e.g. IF Lucy is braver than Samantha, AND Samantha is braver than Rebecca, THEN Lucy is braver than Rebecca?). The second was indeterminate and logically invalid (e.g. IF Chris gets better grades than Helen: AND Chris gets better grades than Dorothy; THEN Helen gets better grades than Dorothy?). Feedback was presented after both questions.

Participants were then administered 24 test questions, with no feedback. Participants were instructed to indicate, quickly and accurately, whether each question was logically valid. There was an equal number of valid and invalid questions. All valid questions were necessarily determinate. Half of the invalid questions were determinate and half were indeterminate.

We analysed the overall percentage of correct responses (i.e. the number of correct responses/total number of questions × 100). The percentage of correct responses was also calculated separately for determinate (n = 18) and indeterminate questions (n = 6).

Neuroimaging investigations

Imaging data were available for 237 patients (n = 232 MRI, n = 5 CT; n = 95 Frontal, n = 71 Posterior). The procedure for lesion tracing and classification is described elsewhere, and summarized in the Supplementary material. The lesion distribution is displayed in Supplementary Fig. 2.

Behavioural analysis

Behavioural analyses were conducted on the 176 patients with lesions falling within frontal or posterior areas and HCs using SPSS version 29 (https://www.ibm.com/spss). Neuropsychological data were assessed for skewness and kurtosis and tested for normality using the Shapiro–Wilk test.

Frontal, Posterior and HC groups were compared on demographic variables, using ANOVA and Fisher's exact test, and performance on neuropsychological tests, ART and DRT, using analysis of covariance (ANCOVA), controlling for age. Following significant differences, *post hoc* tests with Bonferroni correction (alpha 0.05/3 = 0.016) compared Frontal versus Posterior, Frontal versus HC and Posterior versus HC groups.

To investigate potential lateralized frontal effects, Left frontal and Right frontal groups were compared on demographic variables, using *t*-tests and Fisher's exact tests, and performance on neuropsychological tests, ART and DRT, using ANCOVA, controlling for age. Finally, as it has been reported previously that AR performance is more accurate on intra-dimensional than cross-dimensional questions,[36] pairwise comparisons were made using ANCOVA, to compare performance on intra- versus cross-dimensional questions, while controlling for age, in the sample as a whole and in Frontal, Posterior and HC groups separately.

Neuroimaging analysis

Capturing anatomically distributed neural dependence—and disentangling it from the pathology-driven patterns of damage that reveal it—requires a model of the interactions between anatomical loci. Here, we employed a principled and previously validated approach based on statistical models of graphs.[10,48] In brief, the brain is modelled as a network, where each node is an anatomical location and each edge indexes the extent to which its connected nodes share a set of properties. In the context of lesion-deficit mapping, the properties of interest are the presence of damage, the associated cognitive deficit and nuisance factors that could confound their relations. Bayesian stochastic block modelling[10] is used to

infer the hierarchical organization of subnetworks of voxels exhibiting dependence on the behavioural score, disentangled from the incidental spatial structure of lesions. Stochastic block models are non-parametric probabilistic statistical models of the network structure of graphs that enable robust inference to distinct patterns of connectivity arising as a hierarchy of 'blocks' or 'communities' within them.[48,49] In the context of a graph model of the lesioned brain, such communities may be shaped by the neural substrate of the behaviour under study, and/or the anatomical patterns of damage. Layered stochastic block models allow us to disentangle these two distinct types of node connectivity, allowing us to isolate the neural dependents of the task from the incidental pathological structure of the lesions. The procedure is described and validated elsewhere and summarized in the Supplementary material.

Results

Demographics and background tests

The Frontal, Posterior and HC groups were well-matched for age, sex and years of education (all $P > 0.05$; see Supplementary Table 1). The proportion of tumour or stroke patients did not differ significantly between Frontal and Posterior groups or Left and Right frontal groups (both $P > 0.05$). Similarly, lesion volume did not differ significantly between Frontal and Posterior groups or Left and Right frontal groups (both $P > 0.05$). Lesion volume was not significantly correlated with ART, DRT or RAPM performance, nor was it correlated with performance on different types of ART and DRT questions (all $P > 0.05$).

There were no significant differences between any groups in terms of NART, Incomplete Letters, GNT or TROG scores (all $P > 0.05$; see Supplementary Table 2). The Frontal group had significantly lower scores than the Posterior and HC groups on RAPM [$F(2,184) = 20.11$; $P < 0.001$], S fluency [$F(2,151) = 19.79$; $P < 0.001$] and Stroop [$F(2,150) = 10.80$; $P < 0.001$] tests.

A right frontal effect was observed for RAPM performance: the Right frontal group was significantly more impaired than the Left frontal group ($P < 0.05$). Overall, 181 of 247 patients completed the RAPM. Of these, 116 were included in our previous RAPM article[10] and 65 were newly recruited. This sample of 65 patients included 14 with focal right frontal and 10 with left frontal lesions. Reassuringly, in these patients, those with right frontal lesions (mean = 5.64 ± 2.10 SD) had lower RAPM scores than patients with left frontal lesions (mean = 7.30 ± 2.50 SD).

Consistent with previous findings,[50,51] the Left frontal group was significantly more impaired than the Right frontal group on the S fluency and Stroop tests ($P < 0.05$ and $P < 0.01$, respectively).

Analogical reasoning task

On the Perceptual Baseline Matching Task, there were no significant differences between the Frontal, Posterior and HC groups (see Table 1). In contrast, for overall ART performance, there was a significant difference [$F(2,238) = 18.93$; $P < 0.001$], where the Frontal group was significantly impaired relative to the Posterior and HC groups (both $P < 0.001$). An analysis of the lateralized effects showed that the Right frontal group was significantly more impaired than the Left frontal group ($P < 0.05$).

Table 1

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Performance on the Analogical Reasoning Task and the Perceptual Matching Baseline Task

	HC (*n* = 72)	**Frontal (*n* = 100)**	**Posterior (*n* = 70)**	**Left frontal (*n* = 46)**	**Right frontal (*n* = 54)**	**Left posterior (*n* = 31)**	**Right posteri (*n* = 39)**
Perceptual Matching Baseline Task (% correct), mean (SD)	98.61 (5.65)	96.62 (7.19)	97.50 (5.34)	97.15 (7.23)	96.17 (7.20)	98.40 (3.25)	96.79 (6.50)
Analogical Reasoning Task (% correct), mean (SD)	79.40 (11.93)	**67.79**a,***,b,*** **(15.51)**	77.38 (13.51)	73.19 (16.05)	**63.19**c,** **(13.56)**	78.63 (11.87)	76.39 (14.76)
'Progression' rule questions (% correct), mean (SD)	83.22 (12.86)	**71.94** a,***,b,*** **(16.60)**	81.19 (14.52)	75.22 (16.68)	69.14 (16.16)	81.99 (14.54)	80.55 (14.73)
'Odd-one-out' rule questions (% correct), mean (SD)	75.58 (15.09)	**63.71**a,** ,b,*** **(20.06)**	73.57 (17.08)	71.29 (19.29)	**57.25**c,** **(18.53)**	75.27 (14.19)	72.22 (19.15)

Groups are compared using analysis of covariance (ANCOVA), controlling for age. Scores with significant *P*-values are in bold and $^{**}P < 0.01$; $^{***}P < 0.001$. For comparison between Frontal, Posterior and Healthy control (HC) groups, these reflect corrected *P*-values.
SD = standard deviation.

[a]Significant difference from Posterior group.
[b]Significant difference from HC group.
[c]Significant difference from Left frontal group.

For the Progression rule, there was a non-lateralized frontal effect. Thus, the Frontal group was significantly impaired relative to the Posterior and HC groups [ANCOVA: $F(2,238) = 15.20$; $P < 0.001$; *post hoc* tests: both $P < 0.001$]. The performances of the Left and Right frontal groups did not differ significantly.

For the OOU rule, there was a right frontal effect. Thus, the Frontal group was significantly impaired relative to the Posterior and HC groups [ANCOVA: $F(2,238) = 11.74$; $P < 0.001$; *post hoc* tests: $P < 0.01$ and $P < 0.001$, respectively; see Table 1]. Importantly, the Right frontal group was significantly impaired relative to the Left frontal group ($P < 0.01$).

To investigate whether the right frontal effect for the overall ART performance was modulated by difficulty, performance was analysed on intra- and cross-dimensional questions separately. Pairwise comparisons confirmed that performance was significantly more accurate on intra-dimensional than cross-dimensional questions in the entire sample ($P < 0.001$) and in Frontal ($P < 0.05$), Posterior ($P < 0.05$) and HC groups separately ($P < 0.05$). Notably, right frontal effects were observed on both intra- and cross-dimensional questions. Thus, on both, the Frontal group was significantly impaired [ANCOVA: $F(2,238) = 13.21$; $P < 0.001$; ANCOVA: $F(2,238) = 12.45$; $P < 0.001$, respectively] relative to the Posterior (both $P < 0.01$) and HC groups (both $P < 0.001$). Importantly, the Right frontal group was impaired relative to the Left frontal group on both intra- and cross-dimensional questions ($P < 0.05$).

We also analysed performance on questions where rules applied to numerical value, colour or size. For both colour and size, the Frontal group was significantly impaired relative to the Posterior [ANCOVA: $F(2,238) = 6.57$; $P < 0.01$; *post hoc* tests: $P < 0.01$ and $P < 0.05$, respectively] and HC groups [ANCOVA: $F(2,238) = 9.27$; $P < 0.001$; *post hoc* tests: $P < 0.05$ and $P < 0.001$, respectively]. For both colour and size, the Right frontal group was significantly impaired relative to the Left frontal group (both $P < 0.01$). For questions where rules applied to the stimuli's numerical value, there was a non-lateralized frontal effect: the Frontal

group was significantly impaired relative to the HCs [ANCOVA: $F(2,238) = 7.29$; $P < 0.001$; *post hoc* test: $P < 0.001$], but the performances of the Right and Left frontal groups did not differ significantly.

Deductive reasoning task

There was a significant difference between the Frontal, Posterior and HC groups for overall DRT performance [$F(2,142) = 7.73$; $P < 0.001$; see Table 2]. The Frontal group was significantly more impaired relative to the HCs only ($P < 0.01$). The Right and Left frontal groups did not differ significantly.

Table 2

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Performance on the Deductive Reasoning Task

	HC (*n* = 48)	**Frontal (*n* = 55)**	**Posterior (*n* = 43)**	**Left frontal (*n* = 24)**	**Right frontal (*n* = 31)**	**Left posterior (*n* = 19)**	**Right posterior (*n* = 24)**
Deductive Reasoning Task (% correct), mean (SD)	82.79 (15.22)	**71.67**b,** **(15.90)**	79.37 (16.03)	75.88 (14.65)	68.42 (16.29)	77.05 (17.83)	81.21 (14.57)
Indeterminate questions (% correct), mean (SD)	76.06 (25.21)	**55.89**a,*,b,*** **(30.53)**	70.56 (27.60)	65.58 (28.25)	**48.39**c,* **(30.53)**	69.26 (26.18)	71.58 (29.18)

	HC (*n* = 48)	Frontal (*n* = 55)	Posterior (*n* = 43)	Left frontal (*n* = 24)	Right frontal (*n* = 31)	Left posterior (*n* = 19)	Right posterior (*n* = 24)
Determinate questions (% correct), mean (SD)	84.79 (15.42)	**76.69**[b]* **(15.12)**	82.14 (15.17)	79.00 (14.65)	74.90 (15.47)	79.53 (17.26)	84.21 (13.30)

Groups are compared using analysis of covariance (ANCOVA), controlling for age. Scores with significant *P*-values are in bold and *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ (for comparisons between Frontal, Posterior and Healthy control (HC) groups, these reflect corrected *P*-values).
SD = standard deviation.

[a]Significant difference from Posterior group.
[b]Significant difference from HC group.
[c]Significant difference from Left frontal group.

A right frontal effect was also found for indeterminate questions. Thus, the Frontal group was significantly impaired [ANCOVA: $F(2,142) = 7.93$; $P < 0.001$] relative to the Posterior and HC groups ($P < 0.05$ and $P < 0.001$, respectively). Interestingly, the Right frontal group was significantly impaired relative to the Left frontal group ($P < 0.05$). For determinate questions, the Frontal group was significantly impaired relative to the HC group [ANCOVA: $F(2,142) = 4.23$, $P < 0.05$; *post hoc* test: $P < 0.05$] but the Right and Left frontal groups did not differ significantly.

Neuroimaging analysis

The model of ART performance revealed a set of brain communities concentrated in the right middle and inferior frontal gyri, with a hierarchy dominated by caudal middle frontal gyrus (Fig. 2). DRT performance was also strongly right frontal but engaged a more rostral and broadly distributed

network spanning inferior and superior frontal gyri (Fig. 3). RAPM revealed a still more extensive right frontal network, dominated by superior frontal gyrus (Fig. 4). The only comparatively remote region, observed in the ART and RAPM networks, was right dorsal post-central gyrus.

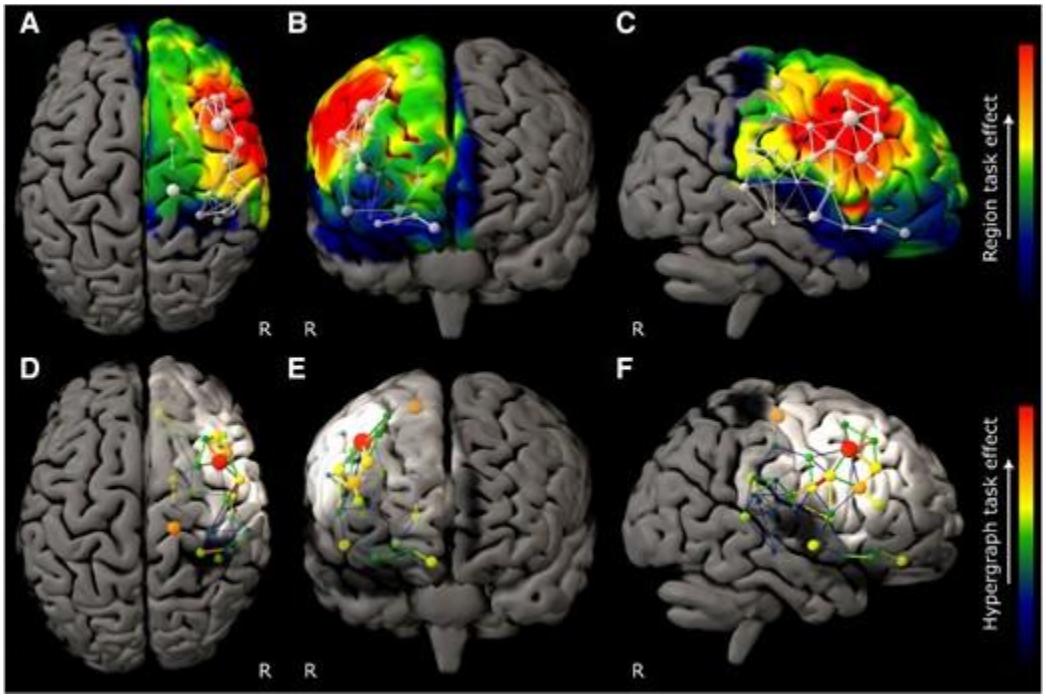

Figure 2

Graph lesion-deficit mapping of Analogical Reasoning Task performance. (**A**–**C**) Backprojection of Analogical Reasoning Task (ART) edge weights onto the brain. (**D**–**F**) The hypergraph at the first agglomerative level shows the inter-community relations between brain regions modulated by performance. The colour map for all plots indexes ART edge weight. The test model exhibited lower entropy—515 399 versus 776 413 nats—than the null model, providing inferential support for distinguishing ART from lesion co-occurrence effects (odds ratio of e261 013 in favour of test). Only regions where 95% confidence intervals did not cross those of the lesion weight distribution are shown.
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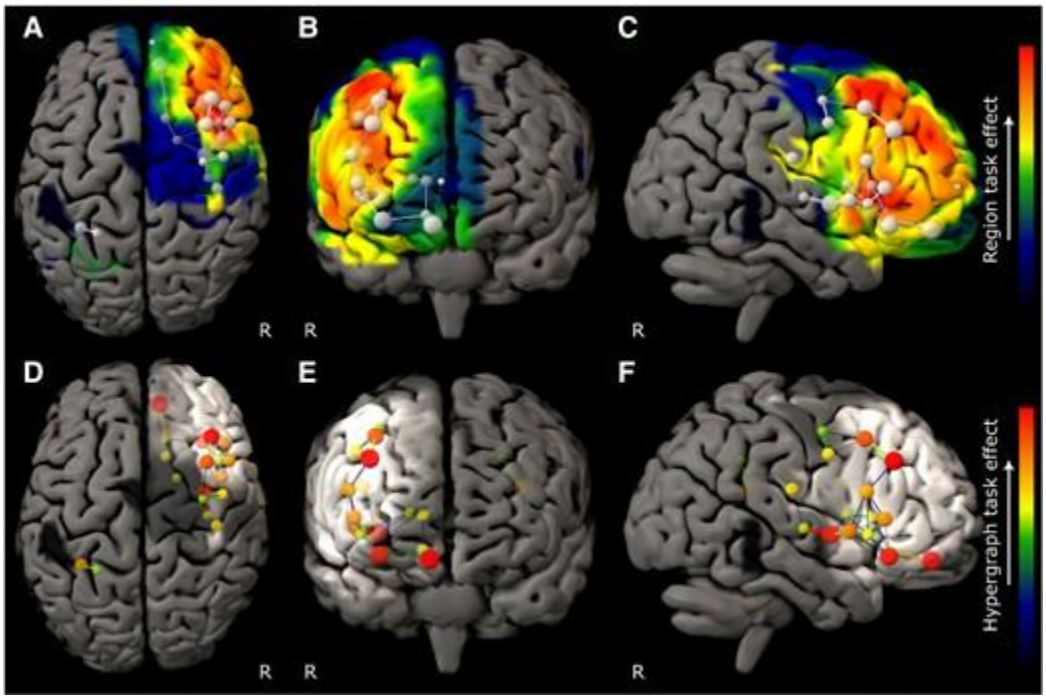

Figure 3

Graph lesion-deficit mapping of Deductive Reasoning Task performance. (**A**–**C**) Backprojection of Deductive Reasoning Task (DRT) edge weights onto the brain. (**D**–**F**) The hypergraph at the first agglomerative level shows the inter-community relations between brain regions modulated by performance. The colourmap for all plots indexes DRT edge weight. The test model exhibited lower entropy—476 362 versus 725 748 nats—than the null model, providing inferential support for distinguishing DRT from lesion co-occurrence effects (odds ratio of e249 386 in favour of test). Only regions where 95% confidence intervals did not cross those of the lesion weight distribution are shown.

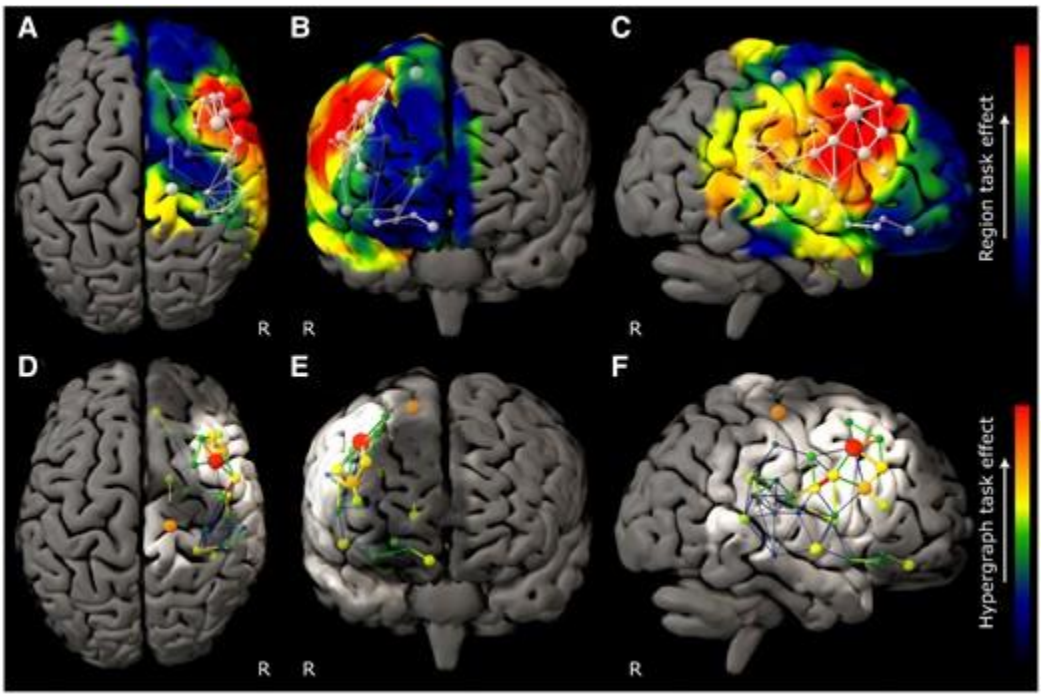

Figure 4

Graph lesion-deficit mapping of Raven's Advanced Progressive Matrices performance. (**A**–**C**) Backprojection of Raven's Advanced Progressive Matrices (RAPM) edge weights onto the brain. (**D**–**F**) The hypergraph at the first agglomerative level shows the inter-community relations between brain regions modulated by performance. The colourmap for all plots indexes the RAPM edge weight. The test model exhibited lower entropy—451 868 versus 699 072 nats—than the null model, providing inferential support for distinguishing RAPM from lesion co-occurrence effects (odds ratio of e247 204 in favour of test). Only regions where 95% confidence intervals did not cross those of the lesion weight distribution are shown.

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Modelling S fluency and Stroop in the same cohort yielded strongly left lateralized networks. S fluency engaged left dorsal superior and middle frontal gyri, in keeping with previous studies (see Fig. 5), and Stroop showed an extensive left frontal network centred on the inferior frontal gyrus, again in line with expectations (see Fig. 6).

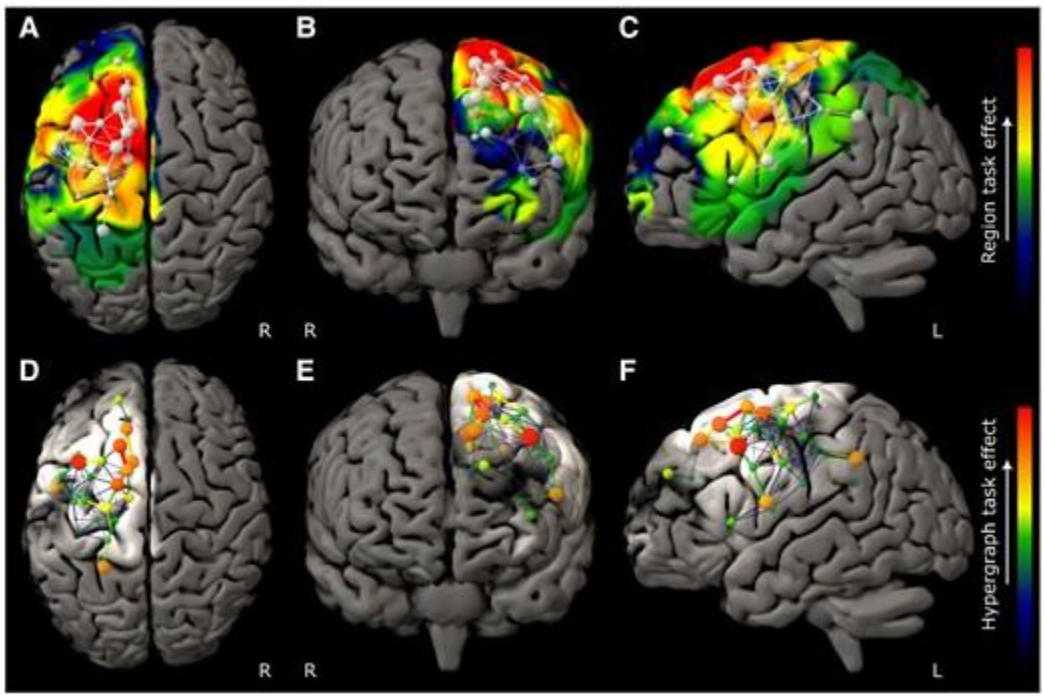

Figure 5

Graph lesion-deficit mapping of S fluency. (**A**–**C**) Backprojection of fluency edge weights onto the brain. (**D**–**F**) The hypergraph at the first agglomerative level shows the inter-community relations between brain regions modulated by performance. The colourmap for all plots indexes the S fluency edge weight. The test model exhibited lower entropy—432 339 versus 646 761 nats—than the null model, providing inferential support for distinguishing S fluency from lesion co-occurrence effects (odds ratio of e214 421 in favour of test). Only regions where 95% confidence intervals did not cross those of the lesion weight distribution are shown.

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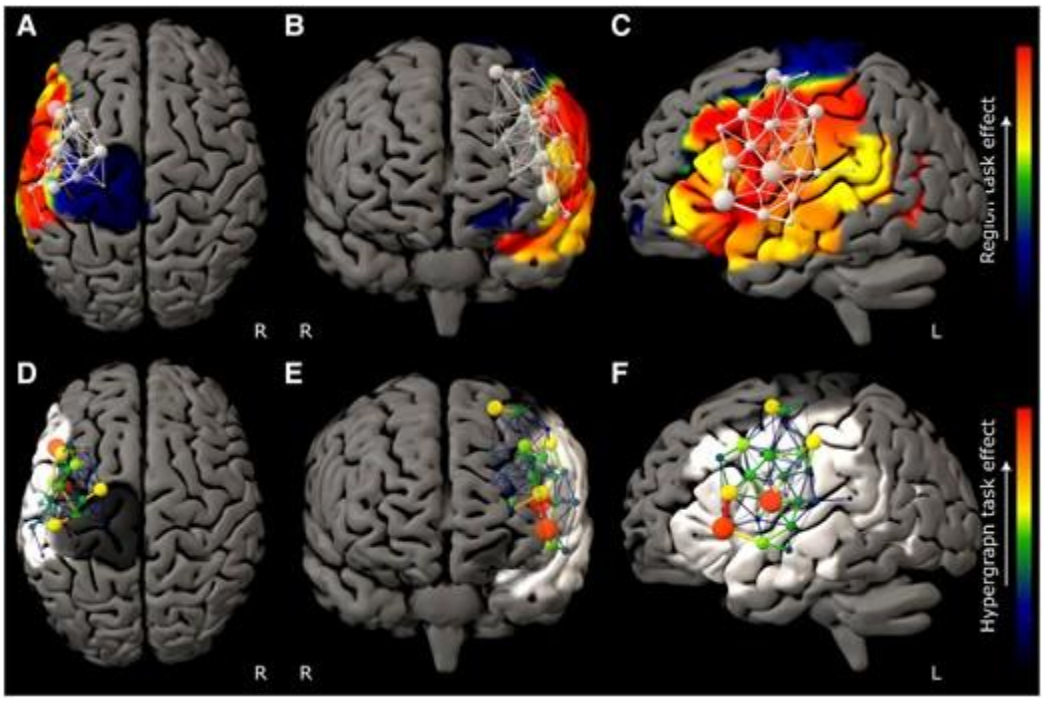

Figure 6

Graph lesion-deficit mapping of Stroop. (**A**–**C**) Backprojection of Stroop edge weights onto the brain. (**D**–**F**) The hypergraph at the first agglomerative level shows the inter-community relations between brain regions modulated by performance. The colourmap for all plots indexes the Stroop edge weight. The test model exhibited lower entropy—440 889 versus 671 673 nats—than the null model, providing inferential support for distinguishing Stroop from lesion co-occurrence effects (odds ratio of e230 783 in favour of test). Only regions where 95% confidence intervals did not cross those of the lesion weight distribution are shown.

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Discussion

To our knowledge, this is the first study to investigate the neural substrates of AR and DR in a large cohort of prospectively recruited patients with unilateral focal frontal or posterior lesions and HCs. We analysed performance on two new tests: the ART and DRT and employed graph lesion-deficit mapping.

The results of our behavioural and neuroimaging analyses converged to implicate a right frontal network in ART and DRT performance. On the ART,

Right frontal patients were significantly more impaired than Left. On the DRT, Right frontal patients were significantly more impaired than Left on questions with indeterminate conclusions but not determinate ones. Graph lesion-deficit mapping implicated a set of predominantly right frontal brain communities in performance on both tests.

The ART and DRT are clearly complex tasks and, hence, likely to rely upon diverse cognitive abilities. Yet, our finding of shared neural dependence suggested reliance upon a common executive process. While the nature of this process is not immediately obvious, consideration of previous theoretical proposals may shed some light. Prado *et al*.,[24] on the basis of data from neuroimaging studies in healthy participants, argued that right frontal and bilateral posterior parietal cortices may support performance on relational DR questions. Notably, both our ART and DRT included relational questions. Hence, the our focal lesion study provided a critical test of the necessity of these brain areas for relational reasoning. Interestingly, we found that posterior parietal cortex made no significant contribution to performance on either test, but the right frontal lobe was critical for both.

Prado *et al*.[24] also suggested that, due to the right hemisphere's well-known dominance in visuospatial processing, predominantly right lateralized areas may be crucial for relational DR performance. This, they argued, is because relational questions can easily be mapped onto a linear continuum and may, therefore, rely on mental representations that are strongly visuospatial. Hence, one may expect right lateralized effects to be evident on DRT determinate questions, where information can be arranged to form a single linear sequence (e.g. IF Lucy is braver than Samantha, AND Samantha is braver than Rebecca, THEN Lucy is braver than Rebecca?). However, if one follows the logic put forward by Prado *et al*.,[24] one may not expect right lateralized effects on indeterminate questions because, for these questions, information contained within the premises cannot be mapped onto a linear continuum. For example, for questions such as 'IF Chris gets better grades than Helen: AND Chris gets better grades than Dorothy; THEN

Helen gets better grades than Dorothy?', the relationships between 'Chris and Helen and Chris and Dorothy' are independent and must, therefore, be considered separately. However, contrary to the aforementioned suggestion about the DRT,[24] we did not find that right frontal patients were significantly impaired relative to left frontal patients for determinate questions. Instead, right frontal patients were significantly impaired relative to those with left frontal lesions for indeterminate questions. Hence, our results broadly agree with the suggestion that the right frontal lobe is critical for relational reasoning questions[24] but do not support the suggestion that they rely on mental representations requiring visuospatial processing.

An alternative suggestion was put forward by Goel *et al.*,[4] who suggested that the left and right frontal lobes may be critical to performance on determinate and indeterminate DR questions, respectively. This proposal was based on a small number of patients ($n < 20$), most with traumatic brain injury: typically associated with diffuse axonal injury.[40] In our large sample of patients with focal unilateral lesion caused by brain tumour or stroke, we found a significant frontal effect but no significant difference between the left and right frontal patients' performances on determinate questions. Our findings suggest that both left and right frontal regions may support cognitive processes involved in generating deductive conclusions on determinate problems. Future research should investigate this further to explore potential more subtle lateralization effects. Our findings are in broad agreement with those reported by Goel *et al.*,[4] who found that their nine right frontal patients were impaired in solving DR indeterminate questions. They suggested that the right frontal lobe supports cognitive processes necessary to represent and maintain uncertainty. Notably, an impairment in representing and maintaining uncertainty is unlikely to explain our right frontal patients' ART performances, since all questions had a determinate solution. Thus, it is plausible that impairment in a different type of executive process from that suggested by Goel *et al.*[4] may underpin our right frontal patients' DRT and ART performances. An analysis of performance on

different types of ART questions may provide insights into the nature of this process.

On the ART, we found that right frontal patients were more impaired than left on questions that followed the OOU but not Progression rule. Notably, the Progression rule—numbers, colours and size increase/decrease progressively—draws upon sequential numerical or perceptual patterns that participants may have encountered previously. In contrast, the OOU rule—stimuli differ in numerical value, colour or size—is likely to be somewhat novel, necessitating active maintenance of the task rule, which must be applied to the source and target sets in parallel. We suggest that both ART OOU questions and DRT indeterminate questions rely upon the ability to actively maintain several novel representations in parallel, which Shallice and Cipolotti[9] held to be a process involving the right prefrontal cortex.

Our findings are relevant to influential theories proposing close links between reasoning abilities and Gf. For example, the influential Cattell–Horn–Carroll theory suggests that Gf is a 'broad' cognitive domain comprising several qualitatively different reasoning abilities, including AR and DR.[6] Interestingly, the results of our graph lesion-deficit mapping showed that the right frontal brain areas critical to ART and DRT performance were remarkably similar to the areas critical for RAPM performance, one of the best-established measures of Gf. This finding supports the notion of a close association between Gf, AR and DR abilities. Strikingly, contrary to the P-FIT and MD network theories that have proposed involvement of posterior brain areas in reasoning,[7,8] we found that ART and DRT performance was unimpaired in posterior patients. Moreover, graph lesion-deficit mapping indicated that the contribution of posterior brain areas was minimal.

Of course, reasoning is complex, and our findings do not imply that other brain areas are not critical for performance on other reasoning tasks. It has been proposed that left frontal areas may be crucial on tests including categorical or

propositional DR questions.[24] Notably, this suggestion was based on neuroimaging evidence, which cannot establish the necessity of brain area for a cognitive function—a limitation that cannot be addressed by further methodological refinement.[29] While a handful of focal lesion studies on reasoning exist, with the potential to offer greater causal power, these have been limited by small samples,[4,35,36,39] inclusion of patients with non-focal lesions[4] and/or the use of VLSM: a methodology with now well-understood flaws.[35-38] We suggest that our strategy of combining graph-based lesion-deficit mapping with detailed investigation of reasoning abilities in a large sample of focally lesioned patients offers a promising methodological approach that can be applied to investigate performance on other tests of reasoning.

It is important to recognize that topological inference in the human brain—from both lesion and correlative data—is inherently challenging. Functional reorganization may have an impact on neural dependence, both in rapidly evolving lesions evaluated in the chronic phase—the commonest experimental scenario—and less rapidly evolving lesions such as tumours. Though adaptation in the former case may be predicted to be less incremental, it is a limitation common to lesion-deficit studies outside the—usually unfeasible—acute context. Where the causal pathology evolves over time, as with tumours, non-stationary effects may be amplified. Nonetheless, there are to our knowledge no known substantive lateralization or rostrocaudal axis differences in tumour progression that could explain the topological differences here. Moreover, our behavioural findings do not suggest that such differences were present. For example, we report robust right lateralized effects for ART, DRT and RAPM performance and, within the same cohort, strongly left lateralized effects for Stroop and phonemic fluency performance.

For the same reason, though the detectability of a lesion-deficit relation will inevitably depend on the interaction between the lesion distribution—not just anatomical location but the high-dimensional pattern of lesion features—and the distributed structure of the underlying neural substrate, that two independent

tasks—Stroop and phonemic fluency—evaluated in the same cohort show robust left lateralization,[50,52-54] demonstrates that the lesion distribution is adequate for identifying left-sided effects.

Equally, since heterogeneous pathological processes do not necessarily respect lobar or any other crude anatomical boundary, we cannot expect the approximate subdivisions into left, right, frontal and posterior groups—defined by >70% of the lesion falling within the defined territory—to coincide perfectly with the graph lesion-deficit maps. We employ high-resolution, multivariate, brain-wide topological inference here precisely because no *a priori* assumptions can be made about the structure of neural dependents—at any scale—and because the task requires the disentanglement of complex behaviourally relevant and incidental anatomical effects. The lesion-deficit model gives us the best inference to the underlying anatomy.

It is unlikely that our right frontal effects on the ART, DRT and RAPM can be explained by potential lateralized specialization for verbal versus non-verbal material. This is because a right frontal network was implicated in performance not only on the ART but, crucially, also on our entirely verbal, DRT. In our sample, of the 239 patients for whom handedness was recorded, only 2.7% of patients were left-handed. However, given the high prevalence of left hemispheric dominance in left-handers, we could not reliably use handedness as an index of dominance, and this is a limitation of our study. A firm answer to this question regarding functional cerebral asymmetries for language and reasoning will require dedicated investigation of a right language dominant cohort.

It is also implausible that our right frontal effects could have arisen due to general task 'difficulty'. Consistent with previous findings, we found that Frontal, Posterior and HC groups were more accurate on ART intra- than cross-dimensional trials.[36] Yet, right frontal patients were significantly less accurate than left on both intra- and cross-dimensional trials.

Our findings suggest that the ART and DRT may provide useful information in clinical practice. To date, only a very small number of clinical tests have been shown capable of detecting right frontal lobe dysfunction.[10,55] Translating the ART and DRT into clinical practice may address this unmet need. Notably, both tests also lack ceiling effects: an issue that applies to many existing neuropsychological tests.[56]

In conclusion, our study represents the most robust investigation of reasoning abilities in patients with single, focal, unilateral lesions. Combining detailed analysis of performance on novel reasoning tests with graph-based lesion-deficit mapping in a large cohort has provided novel insights into the neural basis of reasoning. Our findings imply that a right frontal network is critical for aspects of AR and DR. They also suggest that the ART and DRT are promising new tests, capable of evaluating reasoning abilities and identifying right frontal lobe dysfunction.