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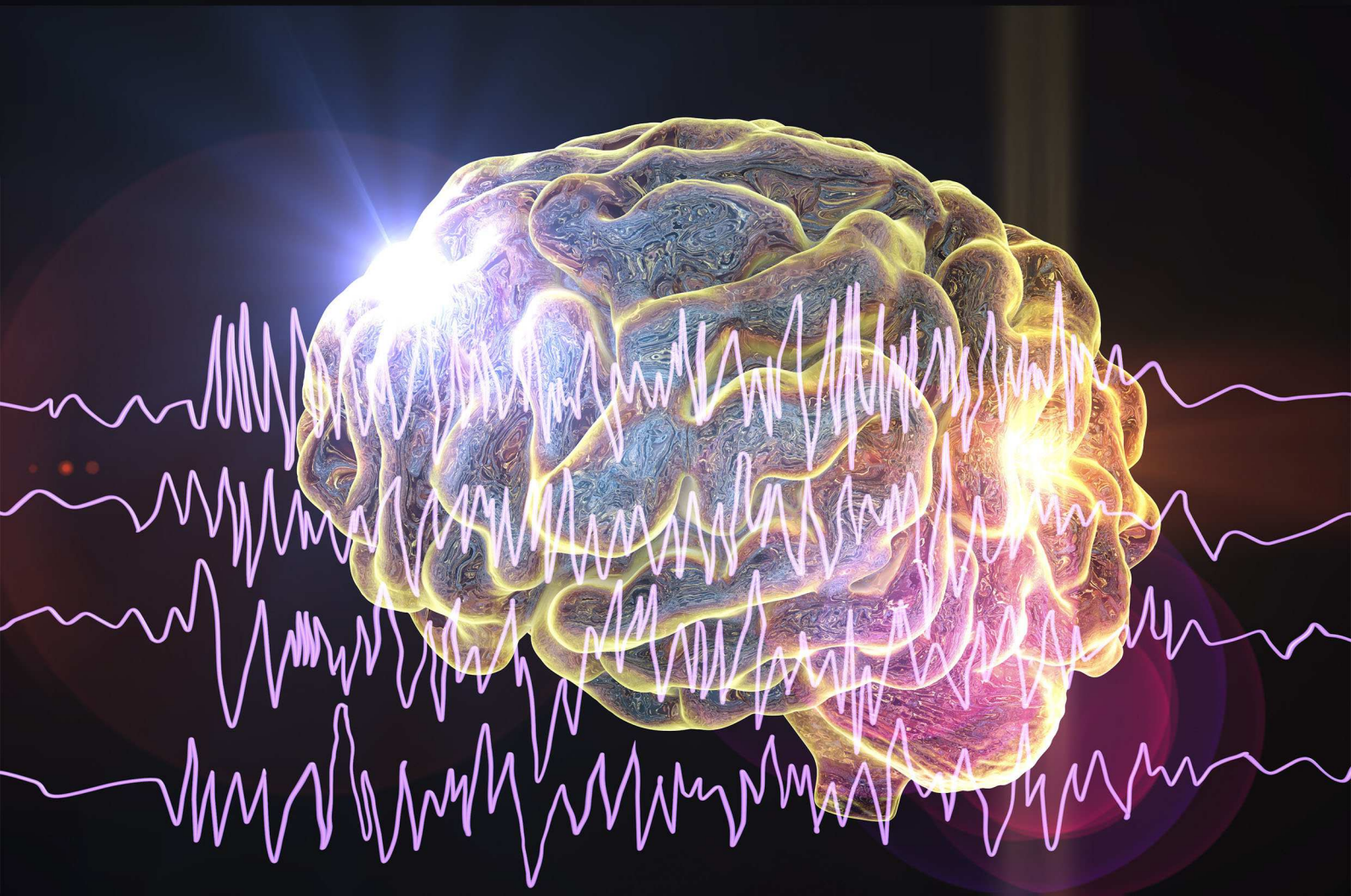

Detecting and Stopping Epileptic Seizures

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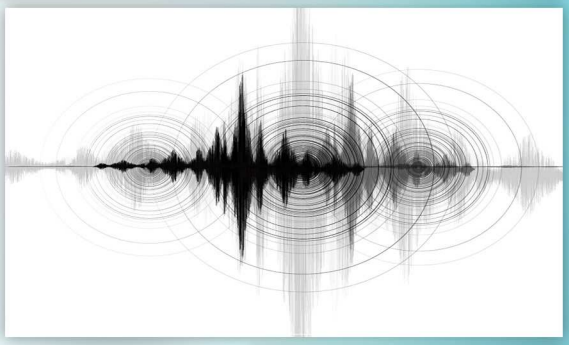


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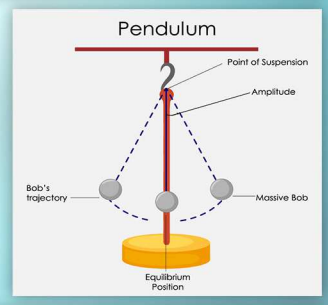
Pendulum
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Equilibrium Position


Ovarian cancer

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NOTE FROM EDITOR-IN-CHIEF

We are excited to bring to you ten articles on recent interesting and relevant scientific discoveries which hold great potential like stopping epilectic seizures, non-addictive painkiller, cure for congenital blindness, predicting earthquake aftershocks and many more.

Hope you find them intellectually stimulating!

Umesh Prasad

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Moderate Alcohol Consumption May Decrease Risk of Dementia

A study suggests that both excessive consumption of alcohol and total abstinence contribute to a person's risk of developing dementia later in life

Dementia is group of brain disorders which affect a person's mental cognitive tasks like memory, performance, concentration, communication abilities, perception and reasoning. Alzheimer's disease is the most common type of dementia usually affecting people who are over 65 years of age. It is a progressive condition which gets worse with time and age affecting memory, thoughts and language and unfortunately there is currently no cure for Alzheimer's disease. It is important to understand the risk factors of dementia, i.e. what makes someone more likely to exhibit dementia as they grow old. The risk of developing Alzheimer's is thought to be dependent on a multitude of factors including heart condition, diabetes, stroke, high blood pressure and high cholesterol.

In an elaborate study published in *British Medical Journal*, researchers from France and UK tracked more than 9000 British civil servants for an average period of 23 years started way back in 1983. When the study was initiated the ages of participants was between 35 and 55 years. Researchers recorded hospital records, mortality registers and access to mental health services to assess participant's dementia status. Along with this, they also recorded each participant's total alcohol consumption at weekly intervals using specifically designed questionnaires. A "moderate" consumption of alcohol was defined as 1 to 14 "units" of alcohol per week. One unit was equal to 10 millilitres. This is the first and only study to conduct a randomized controlled trial -considered as gold standard in medicine - for an extended period of time to analyse the correlation between alcohol and risk of dementia.

Results showed that those participants who drank more than 14 units of alcohol per week, risk of dementia increases as the number of alcohol units consumed increases. Each increase of seven-unit-a-week in consumption was associated with 17 percent increase in risk of dementia. And if the consumption was further increased leading to hospitalization, dementia risk shot up to 400 percent. To the author's astonishment, alcohol abstinence was also associated with 50 percent more risk of developing dementia compared to moderate drinkers. So, both heavy drinkers and abstainers showed increased risk even after setting up controls for age, gender and social and economic factors. This result again emphasizes on a "J-shaped" curve showing correlation between alcohol and dementia risk with moderate drinkers having lowest risk. Moderate alcohol consumption has also been correlated with other better health outcomes including decreased risk of cardiovascular disease, breast cancer etc.

This result is definitely unexpected and very interesting but what are the implications of it. High alcohol consumption can definitely be decreased by a person but does this study absolutely suggest that moderate alcohol consumption is a necessity? Or did some other factors apart from abstinence contribute to increased risk in alcohol abstainers? This is complex discussion and a variety of medical

aspects needs to be consulted before arriving at a generalized conclusion. For example, factors like high blood pressure or heart attack might have led to increased risk in abstainers. Perhaps a variety of factors contribute to dementia risk.

One drawback of this study was reliance on self-reported alcohol consumption because it is clear that people tend to under-report given such circumstances. All participants were all civil servants so finding a generalization is difficult or a separate study needs to be conducted which considers socio-economic factors. Most participants were already in midlife when the study was initiated, therefore, alcohol consumption pattern in early adulthood is completely ignored here. Authors state that their study is mainly observational and no direct conclusion can be made until its scope is expanded.

This work again puts emphasis on midlife risk factors. Changes in someone's brain are believed to start more than two decades before anyone displays any symptoms (example, of dementia). More importance needs to be given to midlife and lifestyle risk factors which can easily be modified right from midlife. Such risk factors are weight, blood sugar levels and cardiovascular health. A person can certainly alter their risk of developing dementia later in life by making suitable changes in midlife. Giving all credit to alcohol consumption for affecting an aging brain would be perhaps gimmicky as more research is needed in examining the brain directly to further our understanding of neurological disorders.

Source

Séverine Sabia et al. 2018, 'Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study', British Medical Journal, vol. 362
DOI: 10.1136/bmj.k2927 ■

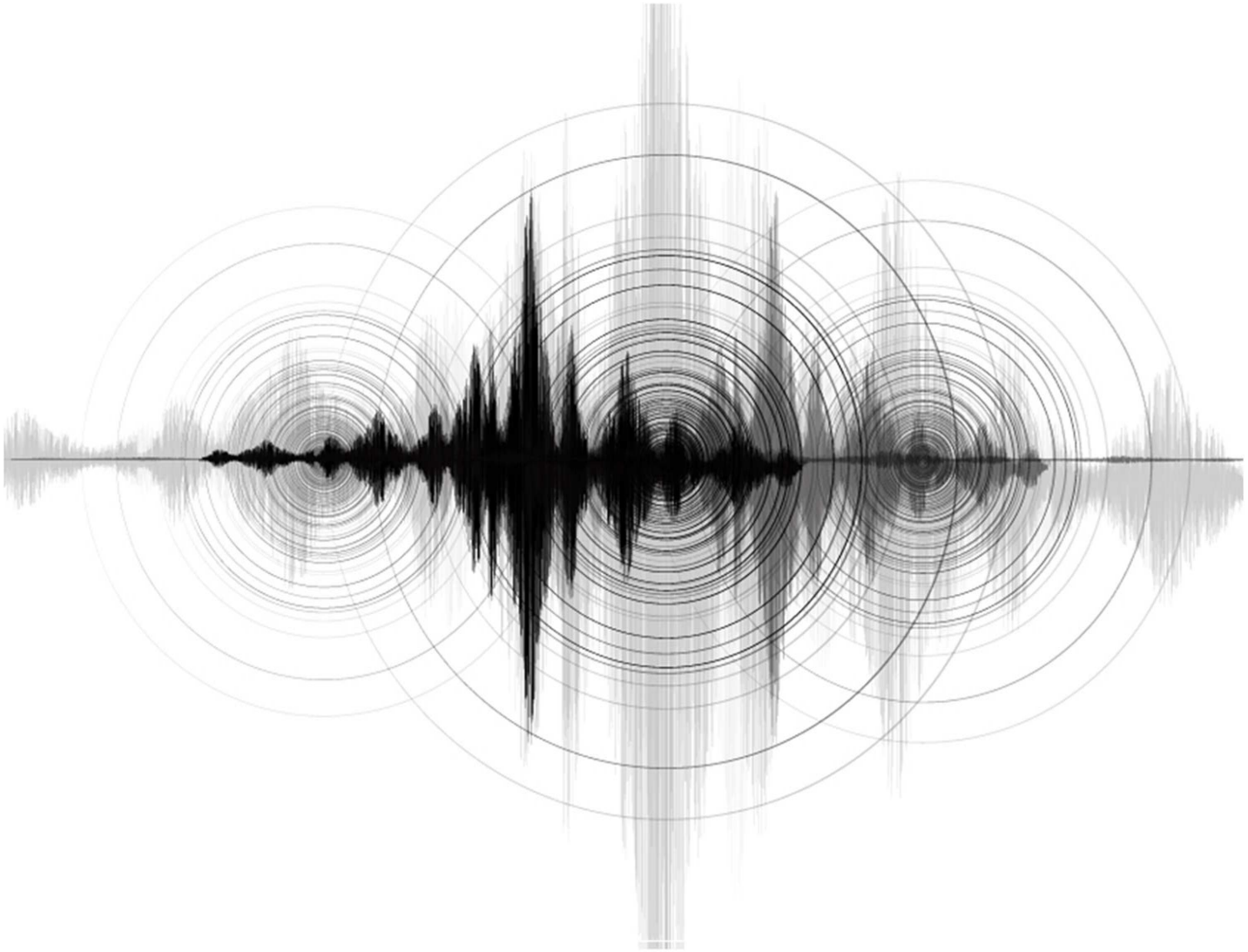
A Novel Method *Which Could Help Forecast Earthquake Aftershocks*

A novel artificial intelligence approach could help predict location of aftershocks following an earthquake

An earthquake is a phenomenon caused when rock underground in the Earth's crust suddenly breaks around a geological fault line. This causes rapid release of energy which produces seismic waves which then make the ground shake which is a sensation we fell during an earthquake. The spot where the rock breaks is called focus of the earthquake and place above it on ground is called 'epicentre'. The energy released is measuredas magnitude, a scale to describe how energetic was an earthquake. An earthquake of magnitude 2 is barely perceptible and can be recorded only by using sensitive specialized equipment, while earthquakes of more than magnitude 8 can cause the ground to noticeably shake very hard. An earthquake is generally followed by many aftershocks occurring by a similar mechanism and which are equally devasting and many times their intensity and severity is similar to the original earthquake. Such post-quake tremors occur generally within the first hour or a day after the main earthquake. Forecasting spatial distribution of aftershocks is very challenging.

Scientists have formulated empirical laws to describe size and time of aftershocks but pin pointing their location is still a challenge. Researchers at Google and Harvard University have devised a new approach for assessing earthquakes and forecasting location of aftershocks using artificial intelligence technology in their study published in *Nature*. They specifically used machine learning, which is one aspect of artificial intelligence. In the machine learning approach, a machine 'learns' from a set of data and after acquiring this knowledge it is able to use this information to make predictions about newer data.

Researchers first analysed a database of global earthquakes using deep learning algorithms. Deep learning is an advanced type of machine learning in which neural networks try and mimic the thinking process of human brain. Next, they aimed to be able to forecast after shocks better than random guessing and try to solve the problem of 'where' the aftershocks will occur. Observations collected from more than 199 major earthquakes around the world were utilized consisting of around 131,000 mainshock-aftershock pairs.



Key Points

- Earthquakes and its aftershocks are devasting because of their intensity and severity.
- Scientists have devised a new approach for assessing earthquakes and forecasting location of aftershocks using artificial intelligence technology which could be an integral part of prediction systems used by seismologists.

This information was combined with a physics-based model which describing how Earth would bestrained and tense after an earthquake which will then trigger aftershocks. They created 5 kilometer-square grids within which system would check for an aftershock. The neural network would then form relationships betweens trains caused by main earthquake and the location of aftershocks. Once the neural network system was well-trained in this manner, it was able to predict location of aftershocks quite accurately. The study was extremely challenging as it used complex real-world data of earthquakes.

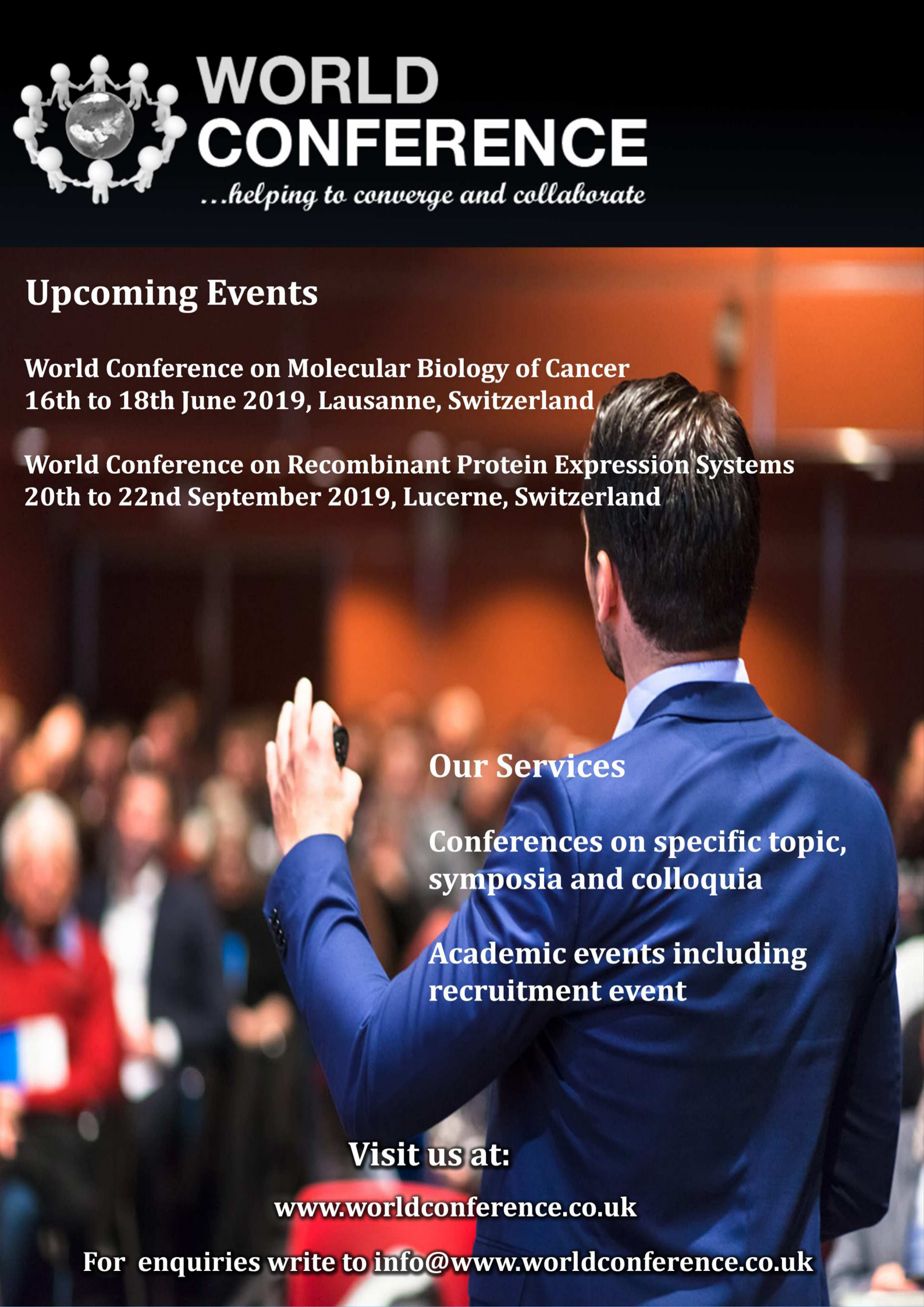
So, researchers alternatively set up artificial and kind of ideal earthquakes to create forecasts and then they examined the predictions. Looking at neural network output, they tried to analyse what different 'quantities' are likely to control forecasting of aftershocks. After doing spatial comparisons, researchers arrived to a conclusion that a typical aftershock pattern was physically 'interpretable'. The team suggests that a quantity called the second variant of deviatoric stress tension – simply called J2 - holds the key. This quantity is routinely used in metallurgy and other fields but has never used before for studying earthquakes. And this quantity is highly interpretable.

Aftershocks of earthquakes cause further injuries, damage properties and also hinder rescue efforts therefore predicting them would be life-saving for humanity. Real time forecast may not be possible at this very moment as there is still a long way to go as researchers pointed out that current AI models can deal with a particular type of aftershock and simple geological fault line only. This is important because geological have different geometry in diverse geographical location on the planet. So, it may not be currently applicable to different type of earthquakes around the world. Never the less, the potential of machine learning is clear. Artificial intelligence technology looks suitable for earthquakes because of n number of variables which need to considered when studying them, example strength of the shock, position of tectonic plates etc.

And neural networks are designed to improve over time, i.e. as more data is fed into a system, more learning takes place and the system steadily improves. In the future, such a system could be an integral part of prediction systems used by seismologists. Planners could also implement emergency measures based upon knowledge of earthquake behaviour. The team also wants to use artificial intelligence technology to predict magnitude of earthquakes.

Source

Phoebe M. R. DeVries, Fernanda Viégas, Martin Wattenberg, Brendan J. Meade. 2018, 'Deep learning of aftershock patterns following large earthquakes', Nature, vol. 7720, no. 632, DOI: 10.1038/s41586-018-0438-y ■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A New Cure for Congenital Blindness

Study shows a new way to reverse genetic blindness in a mammal

Photoreceptors are cells in the retina (back of the eye) which when activated send signal to the brain. Cone photoreceptors are necessary for daytime vision, perception of colours and visual acuteness. These cones expire when eye diseases reach a later stage. And, just like our brain cells, photoreceptors do not regenerate i.e. once they mature they stop dividing. So, destruction of these cells can diminish vision and sometimes even cause blindness. Researchers supported by National Eye Institute of the National Institutes of Health USA have successfully cured congenital blindness in mice by reprograming supportive cells in the retina- called Müller glia - and converting them into rod photoreceptors in their study published in *Nature*. These rods are one type of light receptor cells which are generally used for vision in low light but they are also seen to protect cone photoceptors. Thus, researchers understood that if these rods can be regenerated internally in the eye, this is a possible treatment for many eye diseases in which mainly the photoreceptors get affected.

It has been long established that Müller glia has a strong regenerative potential in other species like zebrafish which is a great model organism for research purposes. Müller glia divide and regenerate in response to injury to the amphibian eye in zebrafish. They also convert into photoreceptors and other neurons and replace damaged or lost neurons. Therefore, zebrafish can again see even after suffering a serious injury in the retina. In contrast, mammalian eyes do not repair the mselves in this manner. Müller glia do support and nourish surrounding cells but they do not regenerate neurons at this pace. After an injury only a very small number of cells are recreated which may not be completely useful. When conducting laboratory experiments, mammalian Müller glia could mimic the ones in zebrafish but only after some injury is made to the retina tissue which is not at all advisable as it will be counterproductive. Scientists looked for a way to reprogram mammalian Müller glia to become a rod photoreceptor without causing any injury to the retina. This would be like mammal's own 'self-repair' mechanism.

In the first step of reprogramming, scientists injected mice's eyes with a gene which would activate beta-catenin protein which triggered Müller glia to divide. In the second step, done after several weeks, researchers injected factors which stimulated the newly divided cells to mature into rod photoreceptors. The newly formed cells were then visually tracked using a microscope. Researchers were ecstatic to find that these new rod photoreceptors that were created were similar in structure to real ones and they could detect incoming light. Additionally, synaptic structures or the network was also formed allowing rods to interconnect with other cells inside the retina in order to relay signals to the brain. To test the functionality of these rod photoreceptors, experiments were done in mice suffering from congenital

blindness, i.e. mice born blind lacking rod photoreceptors which work. While these blind mice did have rods and cones, what they lacked was two critical genes which allow photoreceptors to transmit signals. The rod photoreceptors developed in a similar manner in blind mice having similar function as in normal mice. Activity was seen in part of the brain which receives visual signals when these mice were exposed to light. So, new rods had wired up to successfully transmit messages to the brain. It still needs to be analysed whether new rods had wired up to successfully transmit messages to the brain. It still needs to be analysed whether new rods develop and function properly in a diseased eye where retina cells are do not connect or interact properly.

This approach is certainly less invasive or damaging than other treatments available like inserting stem cells into retina for regeneration purpose and is a major step forward for this field. Experts say that researchers must use a chemical labelling technique to prove that the new functioning rods were created from Müller glia indeed, else the new rods could be from existing photoreceptors who were repaired and their function restored. Authors maintain that they have demonstrated this well, though not by chemical labelling. Experiments are ongoing to assess if mice who were born blind regained the ability to perform visual tasks e.g. running through a maze. At the moment it looks like they perceived light but were not able to make out shapes. Researchers would want to test this technique on human retinal tissue in the laboratory. This study had advanced our efforts towards regenerative therapies for blindness caused by genetic eye illnesses like retinitis pigmentosa, age-related diseases and injuries.

Source

Kai Yao, et al. 2018, 'Restoration of vision after de novo genesis of rod photoreceptors in mammalian retinas', Nature, vol. 560, no. 7719,
DOI: 10.1038/s41586-018-0425-3 ■

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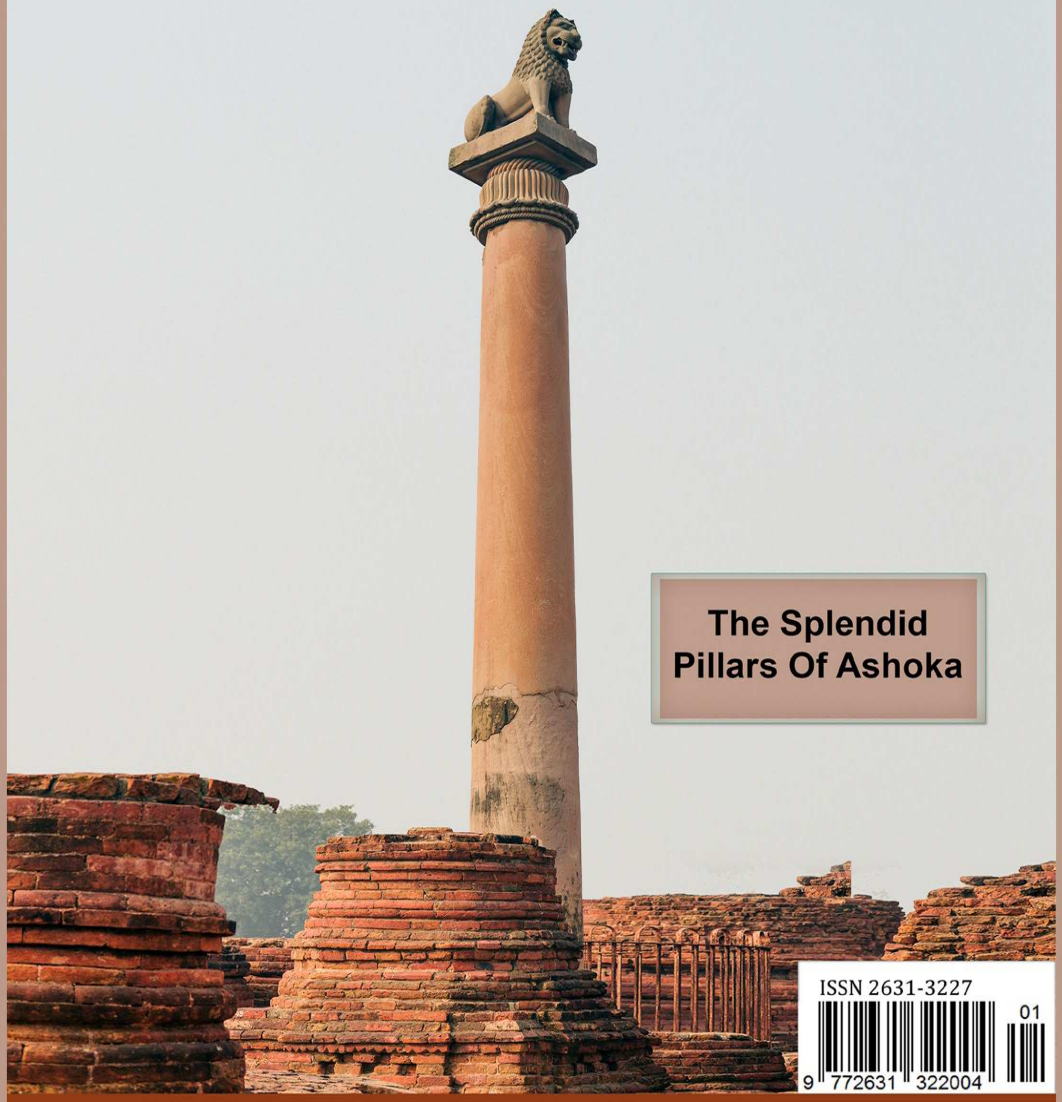

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Detecting and Stopping *Epileptic Seizures*

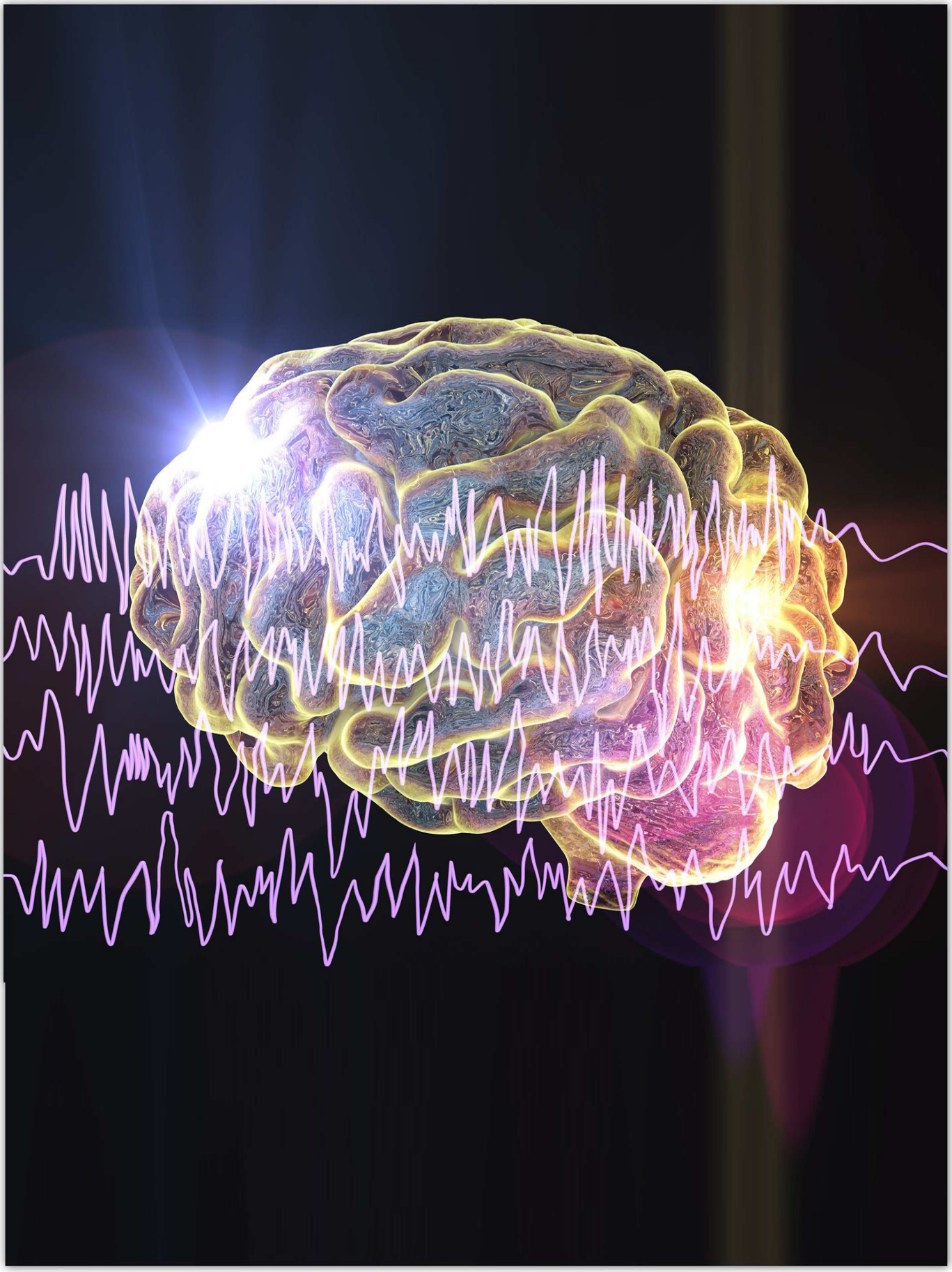
Researchers haves shown an electronic device can detect and end epileptic seizures when implanted into brain of mice

Key points

- A seizure occurs when electrical impulses in the brain escape their normal limits.
- Seizures are signs of different disorders in the brain which cause neurological diseases.
- An electronic device has been discovered which can detect and also end epileptic seizures when it is implanted into brain of a mammal.

Our brain cells called neurons either excite or inhibit other neuronsaround them from sending messages. There is a delicate balance of neurons which 'excite' and the ones which 'stop' the relaying of messages. In the condition called epilepsy - a chronic brain disorder which affects people of all ages and gender -neurons in one's brain start to fire and signal to neighbouring neurons to also fire simultaneously. This causes an escalating effect which leads to imbalance between 'exciting' and 'stopping' activity. The root cause of this electrical activity is thought to be complex chemical changes which occur in nerve cells. A seizure occurs when electrical impulses escape their normal limits. A seizure affects a person's consciousness or motor control. Seizures themselves are not an illness but are signs of different disorders in the brain. Some seizures are not noticeable but some are incapacitating for a person. While there are several kinds of seizures, the above type is associated with epilepsy. Epilepsy is one of the most common neurological disease with around 50 million people suffering from it world wide.The most common treatment for epilepsy is use of epileptic drugs like benzodiazepines which not only have drastic side effects but are also ineffective in preventing seizures in 30 percent of epileptic patients. People with epilepsy and their families have to face stigma and discrimination attached to this disease especially in low- and middle-income countries.

A team of British and French researchers at University of Cambridge, the École Nationale Supérieure des Mines and INSERM have shown an electronic device which when implanted in the brain of mice was able to detect the first sign of a seizure. After this detection, it was able to deliver a native brain chemical inside the brain



which then inhibited the seizure from continuing further. Their innovative study has been published in *Science Advances.*

The electronic device is thin, soft, flexible and made of organic films allowing it to interface well with human tissue. It is also safe as it is seen to be doing minimal damage to the brain. The electrical properties of such organic films make them ideally suited for such medical applications where interface with living tissue is needed. The neurotransmitter or drug in the device targets the origin point of the seizure andthereby signals neurons to discontinue firing. This causes the seizure to stop. A neural probe was used to transport this neurotransmitter to the affected part of the brain. This probe incorporates a mini ion pump and electrodes which monitor the brain activity for the potential seizure. When probe electrodes detect a neural signal belonging to a seizure, ion pump gets activated which then creates an electric field. This electric field enables drug movement across an ion exchange membrane from an internal reserve to outside of the electronic device by a process called electrophoresis which technically allows patients to control dosage and timing of the neurotransmitter drug in a more precise manner. The exact quantity of the drug to be released can be based according to the strength of the electric field. So, this innovative method takes care of 'when' and 'how' much drug needs to be delivered for a specific patient. The drug is delivered without any added solvent solution along which helps in preventing any damage to the surrounding tissue. The drug rather interacts efficiently with cells just outside of the device. Researchers found that only a small amount of drug was required to prevent seizures, this amount was accountedasno more than 1 percent of the entire drug which was initially added into the device. This is helpful as the device will need not to be refilled for lengthy durations. The drug used in this particular study was a native neurotransmitter in our body and it was rather seamlessly consumed by natural developments in the brain immediately upon its release. This suggests that the treatment described should reduce or even eradicate any undesired drug side effects.

The study is definitely promising but it needs to be performed more elaborately in mice to gauge potential side effects and only then can a corresponding study be conducted in humans.It could be a while, several years perhaps, before this device is available in the market for public use.It alsoneeds to be studied whether such a device can prevent seizures altogether. If such a technique succeeds, it could revolutionize medication for epilepsy and also help in other similar illnesses. There is hope that a similar approach could be used for a range of other neurological disorders including brain tumours, strokes and Parkinson's disease.

Source

Christopher M. Proctor et al. 2018, 'Electrophoretic drug delivery for seizure control', Science Advances, vol. 4, no.8, eaau1291,
DOI: 10.1126/sciadv.aau1291

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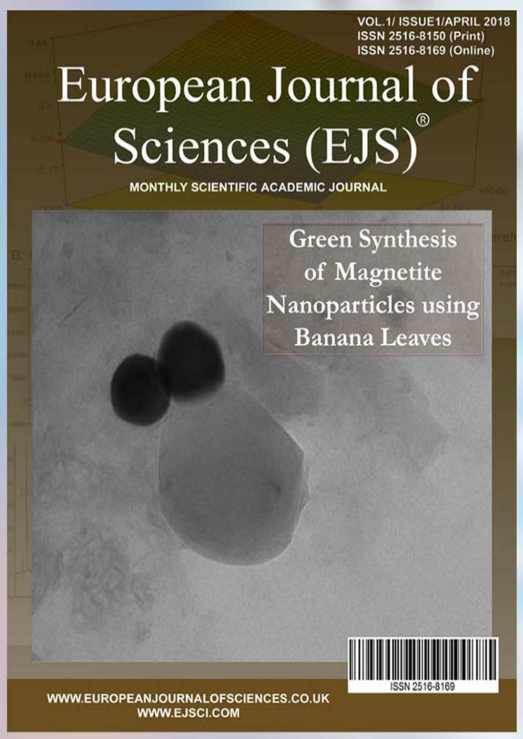
Current Issue



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A New Antibody Approach to Fight Ovarian Cancer

A unique immunotherapy-based antibody approach has been developed which targets cancers consisting of solid tumours.

Ovarian cancer is the seventh most common cancer in women globally. Ovaries are the two reproductive glands that produce eggs in a female and also produce the female hormones estrogen and progesterone. Ovarian cancer is when abnormal cells in ovary start to grow beyond control and make a tumour. Ovarian cancer often has no symptoms in the early stages, so this cancer is generally advanced when it is diagnosed. The five-year survival rate for this cancer ranges from approximately 30 to 50 per cent. If left untreated, the tumour can spread to other parts of the body then called as metastatic ovarian cancer.

Immunotherapy to treat ovarian cancer

Antibody therapy, a type of immune therapy (or immunotherapy), is a 'targeted therapy' in which engineered antibodies are used to identify disease targets, attach to specific substances on cancer cells and then kill them or summon immune cells to kill them. The malignant growths in ovarian cancer do not usually contain liquid or cysts but form solid tumours. A major hurdle in immune therapies for ovarian cancer is that our immune cells cannot infiltrate solid tumours effectively. The success of immune therapies is very limited in solid tumours and this undermines the otherwise highly promising cancer immune therapy approaches.

ers from University of Virginia have developed a novel antibody-approach to kill ovarian cancer by trying to overcome these barriers. In their study published in *Cancer Cell,* authors say the main hurdle is caused due to hostile microenvironment of a solid tumour which makes it difficult for engineered antibodies to reach and kill cancer cells. This microenvironment is low on oxygen and in the case of ovarian cancer a set of large receptors form a protective fence around the cancer cells. Such a challenging environment restricts action of immune cells even after they arrive here. To tackle the problem, authors have designed an antibody with two "heads" and have referred to their method as "single-agent dual-specificity targeting" i.e. this antibody hits two targets on ovarian cancer cell. The first target is folate receptor alpha-1 receptor called FOLR1 – which is highly expressed in ovarian cancer and is an established marker for poor prognosis. Antibody uses FOLR1 for 'anchoring' to the cancer cell. The second target is 'death receptor 5' on cancer cells to which the antibody binds causing cancer cells to die. This engineered antibody was more than 100 times effective in killing cancer cells compared to antibodies which are currently in clinical trials. Researchers have strategically utilized information from large clinical data available for immune therapies for ovarian cancer.

Similar approach in mice also avoids toxicity issues which have been a common issue in previous antibody therapies. For example, liver toxicity is a problem because antibodies leave the bloodstream faste and start to collect in the liver. The antibodies in current study reside in the tumours and therefore 'stay away' from liver. The approach is still in early stages of therapeutic development but researchers want to eventually test this approach in humans. If successful, it could be used for other types of cancer as well in which solid tumours are common like breast and prostrate cancer.

Source

Gururaj Shivange et al. 2018, 'A Single-Agent Dual-Specificity Targeting of FOLR1 and DR5 as an Effective Strategy for Ovarian Cancer', Cancer Cell, vol. 34, no. 2, DOI: 10.1016/j.ccell.2018.07.005 ■

Artificial Wood

Scientists have fabricated artificial wood from synthetic resins which while mimicking natural wood exhibits improved properties for multifunctional use

Wood is an organic fibrous tissue found in trees, bushes and shrubs. Wood can be called as the most useful and maybe the most versatile material on planet Earth. It has been used for thousands of years for multiple purposes and is highly remarked for its low density and high strength. The unique anisotropic cellular structure (i.e. different properties in different directions) of wood grants it amazing mechanical properties as well making it strong, stiff but still light and flexible. Wood has high compressive strength and low tensile strength. Wood is environment and cost friendly, super strong, durable and long-lasting and can be used for building just anything from making papers to building houses.

Nature has already provided us with amazing materials like wood. Yet there is always an inspiration revolving nature for us to design and develop high-performance biomimetic engineering materials, the ones which could 'mimic' the amazing properties of biomaterials already found in nature. The uniqueness of wood comes from its anisotropic cellular structure along with low density and high strength. In the recent past scientists have tried to design materials considering this concept in a bid to duplicate properties of wood like high-strength and light weightness. However, most of the research has led to unsatis factory results as the materials designed suffered from one flaw or the other. It still remains a substantial

Key Points

- Wood found in nature is the most useful and most versatile material on the planet.
- Scientists have fabricated artificial wood which while having similar properties has some significant advantage natural wood like being fire and corrosion resistant.

challenge for engineers to construct artificial wood-like materials. This is of high relevant because it takes decades to grow natural wood and time and efficiency are a strong criterion when looking to make a material similar to natural wood.

Bioinspired wood

Researchers from University of Science and Technology of China have devised a novel strategy for fabrication of bioinspired artificial polymeric wood on a large scale. This artificial material has wood-like cellular microstructure,

good controllability in microstructures and would demonstrate properties like light weightness and high strength analogous to the mechanical properties of natural wood. Researchers state that this new material is as strong as natural wood unlike any other engineered woods researched till date.

Wood found in nature contains a natural polymer called lignin which is responsible for making the wood so strong. This lignin binds small crystallites of cellulose together in a mesh-like structure to create high strength. Researchers thought of replicating lignin by using a synthetic polymer called resol which has similar properties. They successfully converted traditionally available resols (phenolic resin and melamine resin) into artificial wood like material. The conversion was achieved by first utilizing self-assembly properties of the polymer resoland then by under going themocuring. For achieving self-assembly, liquid thermostat resins were unidirectionally frozen, then cured (cross-linked or polymerized) at temperatures no more than 200 degrees Celsius. The engineered wood which this produced adopts a cell-like structure closely resembling that of natural wood. Subsequently, thermocuring– a process consisting of temperature-induced chemical change (here, polymerization) in resol - was performed to produce artificial polymeric woods. The pore size and wall thickness of such a material can be manually controlled. Not just that, the crystallites which resol makes can also be changed based upon the requirement of the type of wood. The colour could also be altered by adding or switching the crystallites which hold resol together. When this engineered wood is compressed, it exhibits resistance similar to its natural counterpart. The approach described in the study can also be termed as a green approach to prepare artificial woods wherein compost of nanomaterials like cellulose nanofibers and graphene oxide can be used. Interestingly, engineered artificial wood displays better corrosion resistance to water and acid compared to natural wood while assuming no decline in its mechanical properties. This means that artificial wood can resist extreme weather eventsand would be improved at providing protection. It also showsbetter thermal insulation and improved resistance to fire and would not catch fire easily like natural wooddoes mainly becauseresol is fire retardant. This can be a boon for sectors like manufacturing construction sector and residential buildings which catch fire when built using natural wood. The material is ideally suited for tough and harsh environments as it is quite enhanced when compared to natural wood. It is also unique when compared to standard engineering materials like cellular ceramics and aerogels with respect to strength and thermal insulation properties. It is also more effective than most plastic-wood composites due to its higher strength. The engineered wood has quite a galore of properties which make it more efficient.

The novel strategy described in this study published in *Science Advances* provides new avenues to fabricate and engineer variety of high-performance biomimetic engineering composite materials which will have some significant advantage over their traditional counterparts. Such novel materials can have broad applications in many fields.

Source

Zhi-Long Yu at al. 2018, 'Bioinspired polymeric woods', Science Advances,
vol. 4, no. 8, eaat7223,
DOI: 10.1126/sciadv.aat7223 ■

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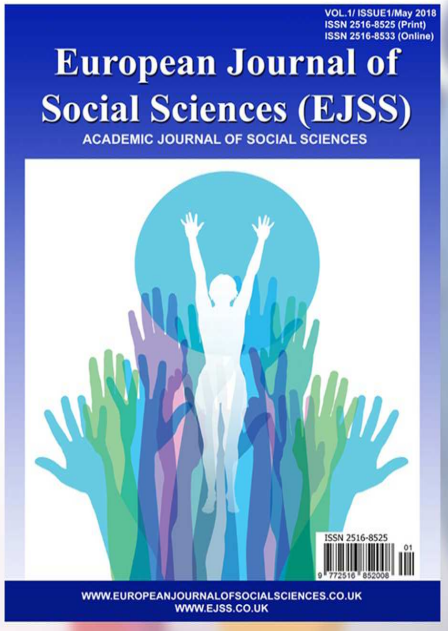
Current Issue



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A New Non-Addictive Pain-relieving Drug

Scientists have discovered a safe and non-addictive synthetic bifunctional drug for relieving pain

Opioids provide the most effective pain relief. However, opioid usage has reached a crisis point and is becoming a huge public health burden in many countries especially in USA, Canada and United Kingdom. The 'opioid crisis' began in the 90s when physicians started prescribing opioid-based pain relievers like hydrocodone, oxycodone, morphine, fentanyl, and several others at a higher rate. As a consequence, prescribed number of opioids are currently at peak levels leading to high consumption, overdose and opioid abuse disorders. Drug overdose is the leading cause of death in younger people who are otherwise disease-free. These drugs are highly addictive as they are accompanied by feelings of euphoria. The most common prescription opioid drugs like fentanyl and oxycodone also produce many undesired side effects.

Scientists have been looking to find an alternative painkilling drug which would be as effective as opioids in relieving pain but minus unnecessary dangerous side effects and risk of addiction. The central challenge of finding an alternative has been that opioids work by binding to a group of receptors in the brain which simultaneously block pain and also trigger feelings of pleasure which causes addiction. In a breakthrough study published in *Science Translational Medicine,* scientists from USA and Japan set out to develop a chemical compound which will focus on two targets i.e. two specific opioid receptors in the brain. The first target is the "mu" opioid receptor (MOP) which traditional drugs bind to, making opioids so effective in relieving pain. The second target is nociception receptor (NOP) which blocks addiction and abuse related side effects of opioids which target MOP. All prescription opioid drugs known work only on

the first target MOP and that it why they are addictive and also show a range of side effects. If a drug can work on both these targets simultaneously that would solve the problem. The team has discovered a novel chemical compound AT-121, which exhibits the required double therapeutic action, in an animal model of non-human primates or rhesus monkeys (*Macaca mulatta*). The study was conducted on 15 adult male and female rhesus monkeys. AT-121 suppresses addictive effects while producing morphine-like analgesic outcome for treatment of pain. The effect is similar to what the compound buprenorphine does for drug heroin. The lower risk of addiction was adjudged by a simple experiment in which the monkeys were given access to self-administer AT-121 by pressing a button, and they chose not to do so. This was in stark contrast to oxycodone, a conventional opioid drug, which the animals would keep administering until they had to be stopped from overdosing. Thus, in this short-term experiment, monkeys did not show any signs of addiction.

Pharmaceutically, AT-121 is a balanced combination of two drugs in a single molecule and thus is being called a bifunctional drug. AT-121 exhibited similar level of effective respite from pain as morphine, but at a dosage hundred-fold lower than morphine. This is an innovative discovery as this medicine was able to relieve pain without risk of addiction and also minus the harmful side-effects which are commonly seen with opioid overdose such as itching and fatal respiratory effects. Similar studies were earlier conducted on mice; however, medicines did relieve pain effectively but they were still addictive and thus were not considered suitable alternatives to existing opioid painkillers.

The current study was conducted in a primate model (monkeys) - a closely related species to humans - making this study more promising with higher probability of similar results in humans. Therefore, compound like AT-121 is a potential viable opioid alternative. Scientists look to conduct further pre-clinical trials to ensure safety of AT-121 before evaluating it in humans. The drug also needs to be tested for 'off-target activity' i.e. any possible interaction it makes with other areas on the brain or even outside the brain. This will help to determine any other likely side effects. The drug shows huge promise as a safe alternative medication for treating pain. If successfully tested on humans, it can help to placate medical burden by making a huge impact on human lives.

Source

Huiping Ding, et al. 2018, 'A bifunctional nociceptin and mu opioid receptor agonist is analgesic without opioid side effects in nonhuman primates', Science Translational Medicine, vol. 10, no. 456, eaar3483,
DOI: 10.1126/scitranslmed.aar3483 ■

The Most Accurate Value of *Gravitational Constant 'G'* ***Till Date***

Physicists have accomplished the first most precise and accurate measurement of Newtonian gravitational constant G

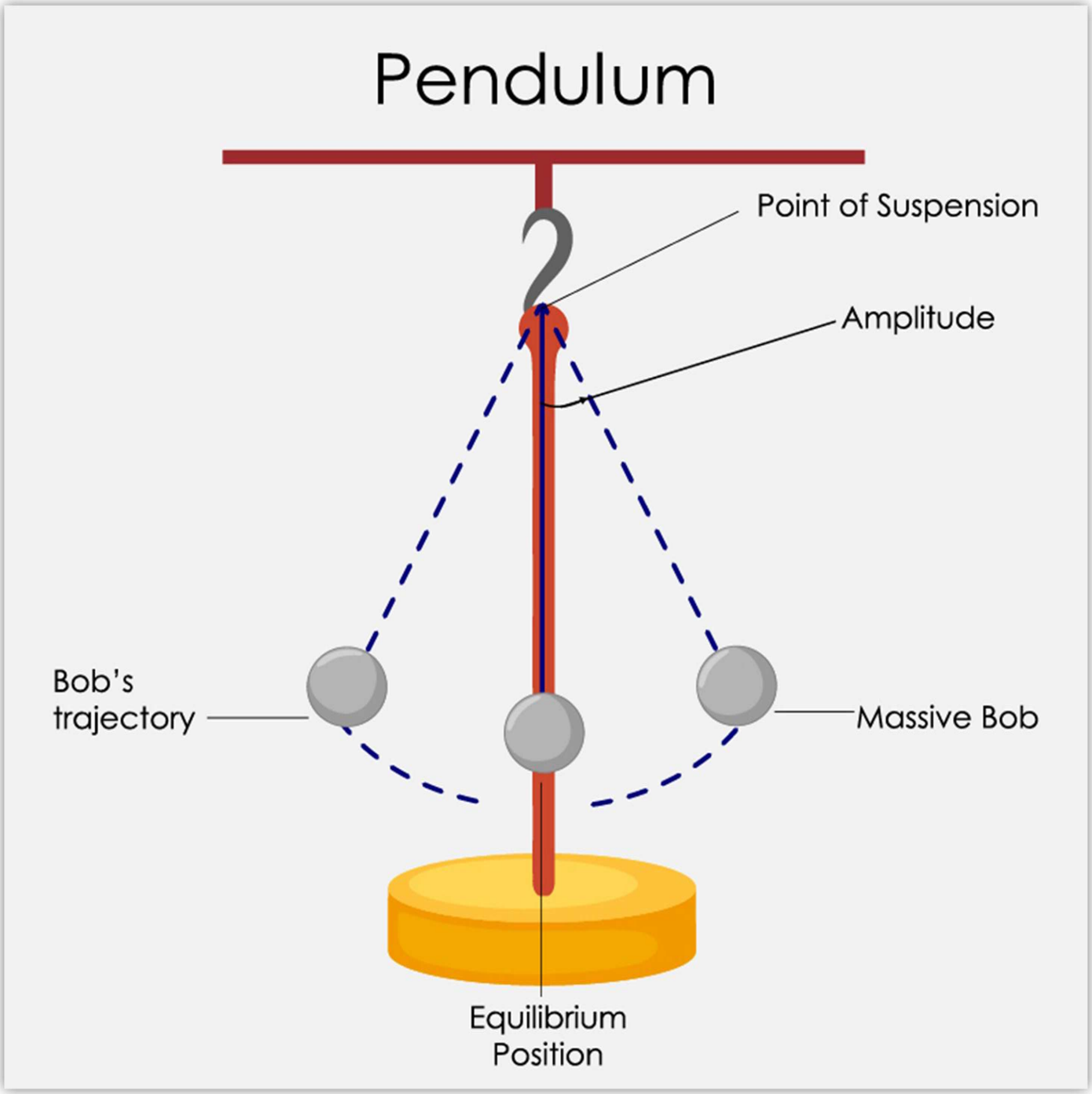
The Gravitational Constant denoted by the letter G appears in Sir Isaac Newton's law of universal gravitation which states that any two objects exert a gravitational force of attraction on each other. The value of Newtoniangravitational constant G (also called Universal Gravitational Constant) is used to measure attractive gravitational forcebetween two objects. It is a good example of a classic yet persistent challenge in physics as even after almost three centuries, it is still not completely clear how can value of G- one of the most fundamental constants in nature - be measured precisely with consistent accuracy. The value of G is determined by measuring the distance and mass of two objects relative to their gravitational attraction. It is an extremely small numerical value owing to the fact that force of gravitational attraction is significantonly for objects with large mass. The most challenging aspect is that gravity is a much weaker force compared to other fundamental forces like electromagnetism, weak and strong attractions and thus G is extremely difficult to measure. And, gravity has no known relationship with other fundamental forces, so calculating its value indirectly using other constants (which can be calculated more precisely) is also not possible.Gravity is the only interaction in nature which cannot be described by quantum theory.

An accurate value of G

In a recent study published in *Nature,* scientists from China have produced the closest results for the value of G. For quite many years before than this study, pre-existing value of G has been $6.673889 \times 10^{-11} m^{-3} kg^{-1} s^{-2}$(Units: meters cubed per kilogram per second squared). In the current study, researchers used angular-acceleration feedback method and also time-of-swing method to be able to come close to constructing a precise and correct value.The results were 6.674184×10^{-11} m^{-3} kg^{-1} s^{-2} and 6.674484×10^{-11} $m^{-3}kg^{-1}$ $s^{-2}$and these results show small standard deviation ever reported when compared to values of G in earlier studies. Standard deviation is used to measure the amount of variation in a set of data. So, a smaller standard deviation means that data are closely distributed to the mean value signifying that there is not much 'deviation' in the data i.e. it does not change much.

The uncertainty around the value of G

Researchers have stated that their results also illustrate "undiscovered systematic errors" in different existing methods. They point out that of all existing methods, the most preferred method involves interferometry – a method of interfering with atomic waves - and this method should be focused on for future improvements. Fresh approaches like shown in this study need



to be adopted to fully understand the mystique of the value of G and its relevance in broad areas of physical sciences. The value of G itself may not be the issue here but the uncertainty which surrounds its value. This shows our inability to measure weak forces such as gravity and lack of theoretical understanding of gravity.

Source

Qing Li et al. 2018, 'Measurements of the gravitational constant using two independent methods', Nature, vol. 560, pp.582–588. ■

Roundworms Revived After Being Frozen in Ice for 42,000 Years

For the first time dormant multicellular organisms' nematodes were revived after being buried in permafrost deposits for thousands of years.

In quite an interesting discovery made by a team of Russian researchers, ancient roundworms (also called nematodes) which had solidified in Siberian permafrost about 42,000 years ago and were frozen since then have come to life again. They existed in late Pleistocene epoch — Ice Age and have been frozen since then. Permafrost is a ground which stays at or below freezing point of water (zero degrees Celsius) continuously for at least two or more years. Such permafrost is mostly located in high altitudes like in and around Arctic and Antarctica regions of the planet. In this study, samples in permafrost were drilled from the frigid ground in north eastern region called Yakutia - coldest part of Russia. Two female roundworms were revived from a large block of ice - which contained around 300 roundworms. One of the two worms is thought to be around 32,000 years old (based upon carbon dating) and came from a soil sample taken from a squirrel burrow 100 feet below ground in the permafrost. The other one, believed to be around 47,000 years old, was found embedded in a glacial deposit just 11 feet below the surface near Alazeya River. Permafrost sediments contain a variety of unicellular organisms – like several bacteria, green algae, yeast, amoebas, moss - which survive for thousands of years in cryptobiosis. Cryptobiosis is defined as a metabolic state entered by an organism when coping with hostile environmental conditions such as dehydration, freezing, and lack of oxygen. These unicellular organisms have been seen to grow again after long-term natural 'cryopreservation'. Cryopreservation is a process which can preserve and maintain biological living organelles, cells and tissues by cooling them at extremely low cryogenic temperatures. This procedure preserves the fine internal structure of cells thus resulting in better survival and maintained functionality.

The study published in *Doklady Biological Sciences* shows for the very first time, capability of a multicellular organism like worm to enter a state of cryptobiosis and remain frozen in permafrost deposits in the Arctic. The samples were isolated and stored in laboratory at around -20 degrees Celsius. The samples were thawed (or "defrosted") and warmed up to about 20 degrees Celsius in Petri dishes containing enriched culture to boost growth. After several weeks, two roundworms woke up from their 'longest nap' and started showing signs of life like normal movement and even started looking for a meal. This can be deemed possible because of some 'adaptive mechanism' by these nematodes. The pair of worms can be called as the oldest living organism on Earth, their age being an average of 42000 years!

The study clearly demonstrates the ability of multicellular organisms to survive long-term cryptobiosis under conditions of natural cryopreservation. Another unique factor is that for the first time this hypothesis has been proven on a record length time-scale as all previous studies have shown that nematodes could survive in extreme environments like freezing temperatures for at least 25 years. There is a strong possibility that other multicellular organisms, including humans, could perhaps

survive cryogenic preservation too.

Though it is now a common practice to 'freeze' one's eggs, or semen for example, to bear children even when one becomes infertile. However, stem cells and other tissues which are very useful for conducting research cannot be preserved through this process. So, successful cryopreservation of different biological samples shall would be critical for any future clinical application or human trials. This technology has been strengthened in past decades with use of superior cryoprotective agents (which protect biological tissue from damage of freezing) and better temperature. Better understanding of freezing and thawing process can advance our understanding of cryo-preservation. Cryogenic freezing remains a controversial topic and borders more towards science fiction. Any talk of an organism being 'asleep' for thousands of years and then springing back to life is baffling and surreal. Looking at this study, it seems like it can be a real and naturally occurring process, at least for worms. If no physical damage is done to the organism and their integrity is maintained in frozen environment then thawing should be possible. Around two decades ago, the same group of researchers had pulled spores and brought them back to life from a single-celled bacterium which were buried inside 250 million years old salt crystals, however, the work is still ongoing and requires more evidence. Such adaptive mechanism used by worms for instance can be of scientific importance for fields of cryomedicine and cryobiology.

Source

A. V. Shatilovich et al. 2018, 'Viable Nematodes from Late Pleistocene Permafrost of the Kolyma River Lowland', Doklady Biological Sciences, vol. 480, no 1, DOI:10.1134/S0012496618030079 ■

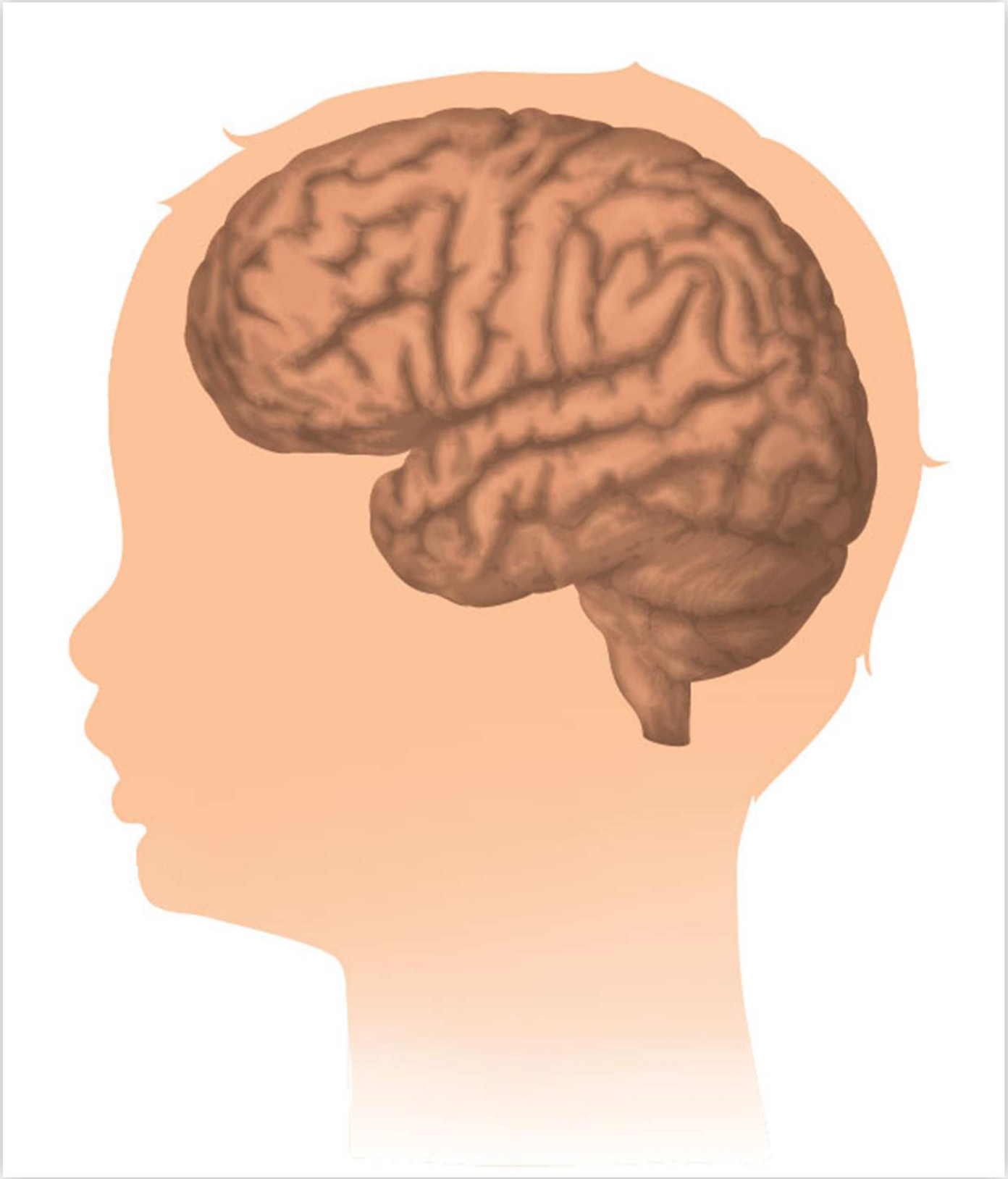
Stress Could Affect *Development of Nervous System* in Early Adolescence

Scientists have shown that environmental stress can affect normal development of nervous system in worms who are approaching puberty

Key points

- Studying our nervous system can further our understanding of different neurological disorders.
- Study in worms shows that stress caused by environmental factors can have a permanent intense effect on connections taking place in the nervous system which is still developing.

Scientists have been trying to understand how our genes (our genetic makeup) and different environmental factors shape our nervous system during early development when we are growing up. This knowledge can further our understanding of different neurological disorders which are mainly caused when normal neural circuits in our nervous system breakdown. In a study published in *Nature*, scientists from Columbia University have studied the nervous system of small transparent worms (*C. elegans*) to elucidate understanding of how it shapes up. They show that stress caused by environmental factors can have a permanentin tense effect on connections taking place in thenervous system which is still developing. In their experiment they made male worms undergo starvation just before the worms were to undergo sexual maturation with an aim to stunt their puberty. Exposure to external stress, specifically starvation, even a few days before sexual maturation affected wiring patterns of critical neuronal circuits in worm's nervous system thus preventing normal changes to take place. The rewiring program of their nervous system was basically interrupted. Once these 'stressed' males underwent puberty and became adult, immature circuits still remained in their nervous system causing them to continue to act immature. Their Immaturity was judged by observing that stressed adult male worms showed high sensitivity to a toxic chemical called SDS compared to normal adult males. The stressed worms also spent limited time with other hermaphrodite worms and had difficulties in mating.



Scientists made this crucial discovery when some worms were accidently left unattended for some weeks and not given food. This led to a pause in worms' normal development and they entered a state called 'dauer state'. This state is like a temporary halt in normal growth of an organism. In case of worms, when immature worms sensed any type of stress, a temporary

pause happens in their normal growth for monthsand later once the stress is gonetheir growth resumes. So, after stress of starvation passed, worms returned to their normal environment and they went on to mature into adults. Upon examining the nervous system of now adult worms, it was seen that some immature connections in male worm's tails were retained which would ideally have been eliminated (or pruned) during sexual maturation. Researchers investigated further to state that 'dauer state' was caused exclusively by stress of starvation and not by any other form of stress. The stress led to remapping of their wire diagrams. Theopposite effects of two neurotransmitters- serotonin and octopamine – control pruning of circuits. The stressed worms had high amount of octopamine which then blocked production of serotonin. If serotonin was given to immature males during stress, then normal pruning took place and adults start exhibiting mature reaction to SDS. In comparison when octopamine was given to immature males, this prevented the circuit pruning. Study suggests that stress can have a likely effect on changes in nervous system when early developmentis taking place. The neurotransmitter serotonin is associated with mental condition of depression in humans. Could this possibility be true for humans also then? It's not straight forward in humans as we have a much larger and more complicated nervous system as compared to animals. Never theless, worms are a simple yet efficient model organisms to study and analyse nervous systems. Lead researchers of this study have initiated a project called ceNGEN through which they will map genetic makeup and activity of each neuron in *C. elegans* worm's nervous system which would help to understand in the makings of nervous system in greater detail and the possible collaboration between one's genetic makeup and one's experiences.

Source

Bayer, E.A. and Hobert, O. 2018, 'Past experience shapes sexually dimorphic neuronal wiring through monoaminergic signaling', Nature, vol. 561,pp.117–121,
DOI: 10.1038/s41586-018-0452-0 ■

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