http://www.bbc.com/news/health-34485090

First 'in womb' stem cell trial to begin

The first clinical trial injecting foetal stem cells into babies still in the womb has been announced.

By James Gallagher Health editor, BBC News website

It is hoped the cells, which are able to transform into a range of tissues, will lessen symptoms of incurable brittle bone disease. The trial, starting in January, will be led by Sweden's Karolinska Institute and in the UK by Great Ormond Street Hospital. The stem cells will come from terminated pregnancies.

Brittle bone disease, officially called osteogenesis imperfecta, affects around one in every 25,000 births. It can be fatal with babies born with multiple fractures. Even those who survive face up to 15 bone fractures a year, brittle teeth, impaired hearing and growth problems.

What are stem cells?

It is caused by errors in the developing baby's DNA -- their blueprint of life -- that mean the collagen supposed to give bone its structure is either missing or of poor quality.

The donated stem cells should provide the correct instructions for growing bone.

Prof Lyn Chitty, from Great Ormond Street Hospital, will carry out genetic testing to search for the defects that lead to the condition. She told the BBC News website: "This is a very serious disease. Our objective is to see if in utero (in the womb) stem cell therapy can ameliorate the condition and the number of fractures."

A type of stem cell which develops into healthy bone, cartilage and muscle will be infused directly into the affected foetuses. Fifteen babies will have the infusion in the womb and again after they are born. A further 15 will only have the treatment after birth and the number of fractures will be compared with untreated patients.

Case Study: -Adam Reynolds

Adam, from Farnborough in Hampshire, was born with broken arms and a fracture in his spine. He says his main problem growing up was "learning to be sensible" when "as a kid you just want to run around and have fun with mates".

Whenever he played football he would have to go in goal to minimise the risk.

He cannot keep track of how many times he's broken his bones, but puts the figure somewhere between 30 and 40.

Adam says he has fewer fractures than other people with osteogenesis imperfecta, but takes longer to heal.

In May 2009 he broke his leg. Six years and 12 operations later it has still not fully recovered. His left leg is four inches shorter than his right.

"Day-to--day life is awkward. If someone stubs their toe on a table they go 'Ow!' - for me it's 'Did I break my toe'?" he says.

But Adam, now 21, does not feel that the condition has held him back in life.

Last week he graduated with a first class honours degree in accounting and finance and is already working. He says: "The idea of a cure coming out or something to help at such an early age is just fantastic news."

Dr Cecilia Gotherstrom, from the Karolinska Institute, told the BBC: "If we could reduce the fracture frequency, strengthen bone and improve growth it would have a huge impact."

Stem cell transplants appear to ease symptoms in children. Starting even earlier when the bone is developing and growing rapidly has the potential to be more effective.

"In--the-womb" foetal stem cell transplants have been tried in two cases of osteogenesis imperfecta. But without a proper clinical trial it is impossible to know how effective the therapy is.

Medical first

Dr Gotherstrom added: "It is the first in--man trial and, if successful, it will pave the way for other pre-natal treatments when parents have no other option."

She said muscle disorders such as Duchenne muscular dystrophy and other bone disorders could one- day benefit from such therapies.

The first infusion will take place 20 to 34 weeks into the pregnancy. This is after the gonads have formed and there should be no risk of the donated cells becoming part of the recipient's sperm or eggs.

Any risk of the donated tissue being rejected in the same way as an organ transplant is thought to be low.

Question of proof?

Commenting on the trial, Dr Dusko Ilic, a reader in stem cell science at King's College London, told the BBC: "Any attempt to help the patients suffering this terrible, debilitating disease is more than welcome."

However, he warned the disease varied so widely from patient to patient that it could be difficult to prove how effective the stem cells were.

He added: "People with the same type of osteogenesis imperfecta may present a different clinical picture, even within the same family.

"At the same time, cellular therapy is unlikely to work to the same extent in different individuals.

"How will we know whether a milder phenotype (symptoms) in a child that received the treatment is natural or is a result of the treatment?"

The trial will start in January and will recruit patients for two years.

http://www.medscape.com/viewarticle/852144

The Placebo Effect: History, Biology, and Ethics

The placebo effect itself is elusive. Though we can hope for it, no one can predict it. Even its definition is ambiguous. The placebo pill—and centuries of various snake oils—has nothing to do with the* placebo effect*, or the difference between the expected effect of a treatment and the one we observe.

Patrick Lemoine, MD, PhD

Introduction and History

The history of placebos is filled with mix-ups and errors. So it is not surprising that the term itself is based on a translation mistake[1]: Jerome was responsible for translating the Bible into Latin (eventually called the Vulgate, meaning it was written in the everyday language of the time), which until then had been in Greek. The soon-to-be saint made a mistake in Psalm 116 (line 9), writing *Placebo Domino*, "I shall please the Lord," rather than *Ambulabo coram Domino*, "I shall walk before the Lord." We should really be talking about the *ambulabo* effect, not the *placebo* effect! But regardless of the term, the history of the placebo marched ahead all the same.

From the 13th century on, bereaved families would chant the verse to pass the time during the recitation of the Office of the Dead. At some point, people began to mock the chanters, branding them as "placebos" for this apparently bizarre behavior. As society became more secular, the lord lost his capital "L" and Placebo was defrocked, instead donning the dress of the courtier. Decidedly pejorative, the word was then used to refer to flatterers and sycophants; in short, all those who sought to please by any means possible.

In the 16th century, a curious method was used to confuse the possessed: the placebo relic. In order to avoid over-the-top exorcisms administered by overzealous clerics, when an individual showed questionable signs of diabolical possession, he or she would be given false relics. If, upon seeing the relics, the "possessed" acted as if they were authentic, the healer deduced that their seizures were the result of their morbid imagination, not the work of the Devil. The idea of controlling a dubious clinical manifestation by administering a treatment that is both inactive and deceiving probably arose from this practice. Until recently, some doctors used placebos to confuse hypochondriacs whose symptoms closely mimicked those of actual maladies and might be triggered, in a very real way, accidentally. We have since learned that this test is not reliable and that it is even dangerous because organic symptoms can react to placebo while the aforementioned functional symptoms may not respond to it. This could cause delays, or even errors, in diagnosis.

In 1752, James Lind (1716-1794), a Royal Navy doctor, published his *A Treatise of the Scurvy* after performing, though he didn't know it at the time, the first experiment to use placebo groups. He devoted the rest of his life to trying to convince the Admiralty—and the school of medicine—of the merits of his discovery. Inventor of what would one day be called the "controlled trial," Lind selected 12 sailors suffering from scurvy. He divided them into groups of two, assigning each group one of six different treatments for 15 days: The first group received cider, the second an elixir of vitriol (sulfuric acid), the third vinegar, the fourth seawater, the fifth lemons and oranges, and the last a mixture of garlic, mustard, and horseradish root. The lucky patients belonging to the fifth group healed within days. Cider also performed miracles but not as quickly, it seems. The other four groups were placebo groups, and the assigned treatment proved fatal. From a moral standpoint, one hopes that Lind did not know for certain that four of his six groups received an inactive product, as he did choose substances that at the time were thought to be therapeutic.

Another example involves Franz Anton Mesmer. In 1784, Louis XVI appointed a commission headed by Benjamin Franklin to evaluate the effectiveness of the physician's famous "baquet," a sort of covered tub that allowed Mesmer to perform magnetic passes for several patients at a time. The conclusion was that "all is not imagination, but [that] the imagination is in everything." Again, it is possible that Mesmer acted in good faith and believed that his tub was effective because in reality it is thanks to his own conviction that he generated spectacular cures for his prestigious patients.

Medicine Embraces Placebo

It took until 1785 to see the word "placebo" appear in the first medical dictionary, the *Motherby's New Medical Dictionary*, where it is defined as "a commonplace medication or method." The word "commonplace" should probably be taken to mean trite. Finally, in 1958, the word placebo appears officially in France in the seventeenth edition of Garnier and Delamarre's *Dictionary of Technical Terms of Medicine* and later in mainstream dictionaries. But it was only with the advent of double-blind controlled trials with random assignment that placebos gained scientific respectability. Up to that point, a sulfurous whiff of quackery hung around the word. The most recent research has also helped to understand how a state of mind, a suggestion, or an expectation on the part of the physician or the patient can induce objective and measurable changes.

In a famous article gathering the data of 15 studies of 1082 patients with extremely varied pain, Beecher[2] showed that a placebo analgesic is effective, on average, in 35.2% of cases, within the range of 4% and 86%. The pain that was the least organic (experimental pain triggered in a laboratory on healthy subjects)

but also the least intense showed the weakest response to the placebo, while particularly distressful organic pain, like angina, proved to be most sensitive to placebo. Indeed, a major driver of the placebo effect is expectations: A healthy person who knows they are experiencing experimental pain that can be stopped whenever they want is surely less motivated to activate a "placebo strategy" than an ill person suffering from a more or less well-controlled but very worrying ailment.

Since Beecher's article was published, many publications have quantified, in disease after disease, the effectiveness of the placebo and the importance of the placebo effect, depending on the patient's and the physician's psychological context. Other research has attempted to provide psychological, ethological, anthropological, or sociological explanations of its mechanisms of action, all based primarily on the suggestion, enthusiasm, and expectation of the doctor, who can induce the patient's reaction himself. Yet it is the biological interpretations that have shed the most unexpected—and convincing—light on this amazing phenomenon that, with the power of thought, can change parameters such as white blood cell count, cholesterol, gastric acidity, pupil size...and so on and so forth!

The Animal Approach

Past work[3] has shown that rats exposed to uncontrollable electric shocks – meaning those from which they cannot escape -- as compared with controllable shocks, demonstrate impaired immune function, as demonstrated by reduced lymphocyte count. This work has also found that simply warning the rats that a shock is coming – by conditioning them with, say, with a flash of light – helps preserve their immune response in response to a grafted malignancy.

Furthermore as one study showed,[4] rats exposed to uncontrollable shocks also exhibit increased susceptibility to malignancy. The researchers divided rats into which malignant cells were grafted into into three groups. The first group served as a control group and was put in a standard cage with no special features. The second batch was put in a cage with a wire mesh floor connected to a generator emitting random electric charges. Given the unpredictability, they had no way to control their stress. The third group was put in a cage equipped with the same device but with a lever that allowed the rats to instantly interrupt the current, both at home and in the second group's cage. The amount of electric shock, pain, and therefore stress was found to be the same in the second and third cages, the only difference being that the rodents in cage number 2 had no control.

After 4 weeks, all of the animals were sacrificed. In cage number 1—the control cage—the tumor had taken hold in 54% of rats; in cage 2, it had grown in 63%; in cage number 3, the cancer took hold in just 27% of the rodents. It is clear from this study that undergoing a painful and stressful stimulus without the possibility for control fosters tumor growth, while the same stress experienced under the same conditions, but with the possibility to control the stimulus, has an anticancerous effect.

A painful, inevitable, incomprehensible, unpredictable event disrupts the immune system and increases the likelihood that an experimental cancer will take; this is the foundation of the nocebo effect (the opposite of placebo), the absence of information and sense of control in animals. Consistent control of the event strengthens the immune system and successfully curbs the development of cancer; this is the placebo effect. Collectively, the aforementioned animal work shows that a systematic warning before a negative event – or a sense of control over a negative situation -- gives subjects time to psychologically prepare and influence their health for the better. Similarly in humans, it has been shown that an enthusiastic and convincing prescription (suggestion) of a placebo can alter many parameters, such as blood pressure, in the long term.[5]

All risky extrapolations aside, the above findings should strongly encourage clinicians to provide their patients with clear, accessible, and tailored information about the diagnosis and the treatments they receive. In humans, the understanding of what will happen makes it possible to control the stress of disease and its treatment.

The Neurobiology of Placebo in Humans

Since 1896,[6] we have known that individuals with allergies sometimes sneeze when exposed to artificial flowers, and in *The Mystery of Placebos*,[5] I described a subject who was allergic to pollen and exposed to intense and prolonged stress (the exodus from Belgium after German invasion in May 1940). The subject did not sneeze for an entire sunny spring, despite his wandering of country roads, confident that he and his family were going to be massacred. The hypothesis is that he experienced an endogenous antiallergic action thanks to significant cortisol and norepinephrine secretion in the face of intense and prolonged terror.

In 1978, Levine[7] demonstrated a possible neurobiological pathway associated with placebo through an original method: After undergoing dental extraction, patients received a placebo analgesic. After a random draw, half of the subjects also received naloxone, an opioid receptor antagonist. The other subjects received a placebo naloxone. The result: The placebo analgesic had no effect on the group receiving naloxone—due to saturated endorphin receptors—whereas it proved effective in those who took a placebo naloxone, whose endorphin receptors remained free. So, in this case, an increase in endorphin transmission explained the pain-killing placebo effect.

This study was controversial until Benedetti[8] confirmed the conclusion. He recruited 340 healthy volunteers and subjected them to ischemic pain of at least a

7 on a 10-point scale, randomly dividing subjects into 12 comparative groups. The study showed a dose-dependent effect of naloxone: The more receptors are blocked, the smaller the placebo effect. This showed definitively the endorphinic system's role in determining the placebo effect on pain.

Endorphins are not the only compounds involved in the complexities of pain physiology. For example, the analgesic effect induced by the placebo may be partially or completely inhibited by cholecystokinin (CCK) and reinforced by a CCK antagonist.[9] Proglumide, one CCK antagonist, was administered postoperatively to patients who were purposely told that this product could increase their pain in order to provoke their anticipatory anxiety. This agent has proved capable of inhibiting nocebo hyperalgesia in a dose-dependent manner, demonstrating the role of CCK in nocebo hyperalgesia. Because CCK is involved in the mechanisms of anticipatory anxiety, it is generally believed that the nocebo effect related to this particular phenomenon is tied to this peptide.

PET scanning also makes it possible[10] to visualize the activation of the anterior cingulate cortex, rich in opioid receptors. Placebo analgesia activates the prefrontal cortex, which can be interpreted as the expression of the subjects' expectations, themselves correlated with doctors' expectations, in anticipation of healing.

Finally, regarding pain, if a patient is conditioned to respond to an opioid analgesic treatment, the placebo effect of morphine is canceled by naloxone. But if the patient is conditioned to a nonopioid analgesic treatment, naloxone does not inhibit the analgesic placebo effect, confirming the idea that the placebo analgesic can only act through an endorphin effect.

Depression and Parkinson Disease

When comparing fluoxetine (Prozac®), venlafaxine (Effexor®), and placebo, quantified electroencephalography showed that placebo responders increase their prefrontal activity sooner and to a greater extent than those who responded to antidepressants and in contrast to resistant patients.[11] PET scan data showed increased metabolic activity, though less intense and in serotonin-rich areas, in placebo responders compared with patients treated with fluoxetine. Moreover, fluoxetine, unlike placebo, activated subcortical, anterior insular, and hippocampal limbic areas, hence the hypothesis that the placebo antidepressant acts on the higher functions rather than the more primitive areas, which makes sense given that it is subjects' expectations, related to consciousness and will, that determine the response or nonresponse to placebo.

A remarkable study[12] published in *Science* showed that the more or less brief placebo effect often observed in this disease corresponds to a release of dopamine in the striatum and that in those who respond to placebo as they do to L-DOPA therapy, this release is comparable, albeit smaller, than that produced by L-DOPA. The placebo effect would therefore be based on activation of endogenous therapeutic substances or medications. Further upstream, dopamine may play a key role because of its involvement in reward pathways in the corticolimbic circuits, including the prefrontal areas, with the expectation of pleasure due to an improvement being a reward in itself. However, it is likely that other neurological and immune systems come into play as well.

Prescribing Placebo Ethically?

There is a saying in medicine that goes double for psychiatry: "You shall not lie." So the question is: Is it possible to prescribe a placebo without lying?

There are two kinds of placebo: a pure placebo and an impure placebo. Pure placebos are substances or interventions with no pharmacologic effect (eg, sugar pills). Impure placebos have pharmacological effects, but their effectiveness for a particular disease is still uncertain. It seems impossible to prescribe a pure placebo without lying, outside of a research context wherein a patient can review the protocol approved by an ethics committee and give their written consent. It's not a problem in this case.

Let's look at sleep: Often when patients try to wean off sleeping pills, they just can't stop that last quarter tablet—it's psychologically difficult to stop. It's a bit like when a child learns to swim and refuses to let go of a floating device that the instructor has gradually deflated!

An easy way to encourage sleep aid-dependent patients to wean off medication involves the ethical use of placebo:

- ***Buy 30 empty capsules (pharmaceutical compounding) from the pharmacy.***
- ***Once you get home, open them all and fill with fine granulated sugar.***
- ***Finally, slip the remaining prescribed quarter tablets into 25 of the empty capsules and close them.***

So there are now 25 *active* capsules that contain a quarter tablet of the prescribed sleeping aid and 5 capsules of pure placebo. Now mix the capsules and take one each night. The second month, prepare 20 sleeping aid capsules in the same way described and 10 placebo capsules; the third month, 15 sleeping aid capsules, 15 placebo capsules; and so on and so forth until there is (almost) nothing left but placebo capsules.

Usually, by this point, weaning is complete, and you can stop entirely. But I do recall one of my patients, a specialist doctor, who for several years continued to take his capsule each night even though there was only one capsule in the month's supply containing a sleeping aid and 29 or 30 capsules of placebo. "It helps me," he said "to know that each night I have even the slightest chance of having my

sleeping aid." And it's true that he was able to establish a healthy sleeping pattern after 10 years of taking a sedative hypnotic each night. I always let him do as he wished—taking a quarter tablet of a sleeping aid per month really doesn't pose a problem.

And how about impure placebos? Can you prescribe a medication without lying by using it for something other than its official use? Think of the way vitamin C is used to treat maladies other than scurvy, even though there is no scientific proof that it is the least bit effective in other applications.

I think the answer is yes, if the prescriber believes in it. This could be seen as both provider and patient under the influence of expectation. Take the example of homeopaths, who are able to maximize the placebo effect.

Conclusions

Our brain is the administrative headquarters of a formidable, unbelievable pharmaceutical company able to demand and distribute its products throughout our body. We manufacture multitudes of medications: antibiotics, antimitotics, painkillers, antipyretics, anxiolytics, antidepressants, anti-inflammatories, immunostimulants, anticholesterols, antihypertensives, antipsychotics, cancer drugs, and more. We can also activate other parallel circuits involving natural counterparts to more culturally and medically scandalous substances: anandamide (cannabis), alcohol, amphetamines, nicotine, cocaine, LSD, endorphins, and more. The president of this whole enterprise is "me"; our brains; each of us.

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Red wine with dinner can improve cardiovascular health of people with type 2 diabetes

Both red and white wine can improve sugar control depending on genetic profile

BEER-SHEVA, Israel - A glass of red wine every night may help people with type 2 diabetes manage their cholesterol and cardiac health, according to new findings from a two-year randomized controlled trial (RCT) led by researchers at Ben-Gurion University of the Negev (BGU). Additionally, both red and white wine can improve sugar control, depending on alcohol metabolism genetic profiling.

In this first long-term alcohol study, just published in the prestigious Annals of Internal Medicine, the researchers aimed to assess the effects and safety of initiating moderate alcohol consumption in diabetics, and sought to determine whether the type of wine matters.

People with diabetes are more susceptible to developing cardiovascular diseases than the general population and have lower levels of "good" cholesterol. Despite the enormous contribution of observational studies, clinical recommendations for moderate alcohol consumption remain controversial, particularly for people with diabetes, due to lack of long-term, randomized controlled trials, which are the "holy grail" of evidence-based medicine.

"Red wine was found to be superior in improving overall metabolic profiles, mainly by modestly improving the lipid profile, by increasing good (HDL) cholesterol and apolipoprotein A1 (one of the major constituents of HDL cholesterol), while decreasing the ratio between total cholesterol and HDL cholesterol," the researchers explain.

The researchers concluded that "initiating moderate wine intake, especially red wine, among well-controlled diabetics, as part of a healthy diet, is apparently safe, and modestly decreases cardio-metabolic risk. The differential genetic effects that were found may assist in identifying diabetic patients in whom moderate wine consumption may induce greater clinical benefit."

The researchers also found that only the slow alcohol-metabolizers who drank wine achieved an improvement in blood sugar control, while fast alcohol-metabolizers (with much faster blood alcohol clearance) did not benefit from the

ethanol's glucose control effect. Approximately one in five participants was found to be a fast alcohol-metabolizer, identified through ADH enzyme genetic variants tests.

Wine of either type (red or white) did not effect change in blood pressure, liver function tests, adiposity, or adverse events/symptoms. However, sleep quality was significantly improved in both wine groups, compared with the water control group. All comparisons were adjusted for changes in clinical, medical and drug therapy parameters occurring among patients during the years of the study.

The two-year CArdiovaSCulAr Diabetes and Ethanol (CASCADE) randomized controlled intervention trial was performed on 224 controlled diabetes patients (aged 45 to 75), who generally abstained from alcohol. They gradually initiated moderate wine consumption, as part of a healthy diet platform, and not before driving. The trial completed with an unprecedented adherence rate of 87 percent after two years.

According to BGU's Prof. Iris Shai, principal investigator of the CASCADE trial, and a member of the Department of Public Health in the Faculty of Health Sciences, "The differences found between red and white wine were opposed to our original hypothesis that the beneficial effects of wine are mediated predominantly by the alcohol. Approximately 150ml of the dry red or white tested wines contained ~17g ethanol and ~120kCal, but the red wine had sevenfold higher levels of total phenols and 4 to 13-fold higher levels of the specific resveratrol group compounds than the white wine. The genetic interactions suggest that ethanol plays an important role in glucose metabolism, while red wine's effects additionally involve non-alcoholic constituents. Yet, any clinical implication of the CASCADE findings should be taken with caution with careful medical follow-up."

The study was performed in collaboration with Prof. Meir Stampfer from Harvard University, USA, and with colleagues from University of Leipzig, Germany and Karolinska Institute, Sweden.

In the new study that followed the research group's three-month alcohol pilot RCT findings (Shai I, et al., Diabetes Care 2007), the patients were randomized into three equal groups according to whether they consumed a five-ounce serving (150ml) of mineral water, white wine or red wine with dinner every night for two years. Wine and mineral water were provided free of charge for the purposes of the study. Compliance with alcohol intake was tightly monitored, with patients returning their empty wine bottles and receiving their new supplies. All groups followed a non-calorie-restricted Mediterranean diet (following the group's previous two-year dietary RCT findings; Shai I, et al., NEJM 2008). Adherence was monitored using several validated assessment tools.

During the study, subjects underwent an array of comprehensive medical tests, including continuous monitoring of changes in blood pressure, heart rate and blood glucose levels, and follow-up for the dynamic of atherosclerosis and fat by ultrasound and MRI tests.

The study was funded by a grant from the European Foundation for the Study of Diabetes (EFSD) of the European Association for the Study of Diabetes (EASD).

American Associates, Ben-Gurion University of the Negev (AABGU)

AABGU plays a vital role in sustaining David Ben-Gurion's vision, creating a world-class institution of education and research in the Israeli desert, nurturing the Negev community and sharing the University's expertise locally and around the globe. With some 20,000 students on campuses in Beer-Sheva, Sede Boqer and Eilat in Israel's southern desert, BGU is a university with a conscience, where the highest academic standards are integrated with community involvement, committed to sustainable development of the Negev. AABGU is headquartered in Manhattan and has nine regional offices throughout the United States. For more information, visit http://www.aabgu.org.

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Cardiff University study on the science of hallucinations

Scientists at Cardiff University believe they can help explain why some people are prone to hallucinations.

Researchers worked with colleagues at the University of Cambridge to study the predictive nature of the brain. They looked at the idea that hallucinations happen due to the brain's tendency to interpret the world using prior knowledge and predictions. The study examined whether the brain creating this image of the world contributes to people's psychosis.

Research published on Monday in the journal Proceedings of the National Academy of Sciences studied 18 people who suffered from very early signs of psychosis who had been referred to a mental health service run by the Cambridgeshire and Peterborough NHS Foundation Trust.

'Broken' brain

They compared them to 16 healthy volunteers and asked them if they could make sense of vague black and white images. All of them were then shown the full colour original picture to improve the brain's ability to understand the ambiguous

image. There was a larger performance improvement in people with early signs of psychosis compared to the healthy control group.

The University of Cambridge's Naresh Subramaniam said: "These findings are important because, not only do they tell us that the emergence of key symptoms of mental illness can be understood in terms of an altered balance in normal brain functions.

"Importantly, they also suggest that these symptoms and experiences do not reflect a 'broken' brain but rather one that is striving - in a very natural way - to make sense of incoming data that are ambiguous."

Look at the picture. Can you see anything? **Image copyright Cardiff University**

Picture perfect?

Now look at the photograph below before taking another look. Scientists say it is likely that you can now make sense of it. It is the brain's ability to fill in the blanks that could help explain why some people suffer from hallucinations.

One of the study's authors, Dr Christoph Teufel, from Cardiff University, said: "Vision is a constructive process - in other words, our brain makes up the world that we 'see'. "It fills in the blanks, ignoring the things that don't quite fit, and presents to us an image of the world that has been edited and made to fit with what we expect."

An example of this would be a person walking into their living room and identifying a fast-moving black shape as their cat, despite the fact the visual information was no more than a blur. The sensory input was minimal and prior knowledge did the creative work.

Prof Paul Fletcher of the University of Cambridge said: "Having a predictive brain is very useful - it makes us efficient and adept at creating a coherent picture of an ambiguous and complex world.

"But it also means that we are not very far away from perceiving things that aren't actually there, which is the definition of a hallucination."

He added that "altered perceptual experiences" are not limited to people with mental illnesses, but have been seen in a milder form across the whole population.

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Brain's activity map makes stable 'fingerprint'

Neuroscientists have found that they can identify individuals based on a coarse map of which brain regions "pair up" in scans of brain activity.

By Jonathan Webb Science reporter, BBC News

The map is stable enough that the researchers could pick one person's pattern from a set of 126, by matching it to a scan taken on another day.

This was possible even if the person was "at rest" during one scan, and busy doing a task in the other.

Furthermore, aspects of the map can predict certain cognitive abilities.

Presented in the journal Nature Neuroscience, the findings demonstrate a surprising stability in this "functional fingerprint" of the brain.

"The exciting thing... is not that we can identify people by putting them in an MRI machine - because we can identify people just by looking at them," said Emily Finn, a PhD student at Yale University who co-wrote the study with her colleague Dr Xilin Shen.

"What was most exciting to me was that these profiles are so stable and reliable, in the same person, no matter if it's today or tomorrow and no matter what your brain is doing when we're scanning you."

Predicting intelligence

Crucially, this fingerprint is based on brain activity - not the organ's physical structure.

In the the myriad links between our billions of brain cells, and even at the level of a normal MRI scan, we are all physically unique.

But Ms Finn and her colleagues drew a map of each brain purely on the basis of which regions, in each individual, tended to leap into action at the same time. They used data from functional MRI (fMRI), which records subtle ups and downs in the busyness of the brain.

Because it is relatively imprecise, fMRI has not typically been used to compare individual brains. Instead, scientists tend to record from several subjects and average the results.

"We were interested in flipping the traditional fMRI analysis on its head, and not asking what are the commonalities - how do all brains look the same, doing the same task - but rather, does the same brain look the same, regardless of what it's doing?" Ms Finn explained.

So they took fMRI results from the first 126 subjects of the Human Connectome Project, a huge US initiative to gather data about the brain's "wiring diagram". These subjects had all been scanned multiple times, on different days, both while they were resting and while they were occupied by various tests.

Within each of those scans, the researchers looked at what was happening in 268 key spots within the brain: how closely did the ups and downs at this spot match the ups and downs at all 267 other spots?

This produced a profile of the flow of activity in each brain. And that profile was consistent enough that the team could use it to pick out the same individual - more than 90% of the time - from a different set of scans, done on a different day.

They also found that they could use the profile to predict, to a certain degree, how well the subjects did at particular cognitive tests that measured "fluid intelligence". This is a type of on-the-spot, untrained reasoning that is measured by some IQ tests. Ms Finn is quick to point out that her technique could never substitute for those questionnaires.

"None of us would recommend a brain scan over an IQ test," she said. "This is just proof-of-concept that these connectivity profiles are relevant to this very sophisticated cognitive behaviour."

If these individual maps show strong associations with psychological phenomena, she added, they could prove useful in the clinic.

"This opens the door to predicting things that are harder to tell just by looking at someone, or giving them a test - like risk for different mental illnesses."

Ones and zeros

Recently, a different study used a very similar technique to show that these brain maps can predict a range of characteristics, from someone's vocabulary to their income.

One of its authors, Prof Thomas Nichols, said he was not surprised that Ms Finn and her colleagues were able to distinguish individuals.

"What this is getting at is the very high-quality nature of this data," said Prof Nicholls, a brain imaging statistician at the University of Warwick. He said the data emerging from the Human Connectome Project, which also formed the basis of his study, is "bleeding-edge, state-of-the-art" stuff.

"It's really, really good and there's a huge volume of data on each subject."

Tim Behrens, professor of computational neuroscience at Oxford University, said he was most impressed by the consistency between the resting and task-based maps in the study.

"What is particularly interesting is that the way the brain connects… at rest, is so similar to how it connects during a task - when it's doing something interesting. That's what's exciting about it," Prof Behrens told the BBC.

By comparison, he said, you would not expect "the pattern of ones and noughts" in a busy computer to reflect the pattern in a computer that is not doing anything.

"It tells you that something about the function of the brain is fundamentally built into patterns of activity that just live there, all the time."

http://www.eurekalert.org/pub_releases/2015-10/uobc-dds100815.php

Destructive disease shows potential as a cancer treatment

Scientists at the University of British Columbia, Vancouver Coastal Health and the BC Cancer Agency have discovered a protein from malaria that could one day help stop cancer in its tracks.

This new approach, which halted the growth of various tumours in mice, was based on a discovery by collaborators at the University of Copenhagen. While exploring why pregnant women are particularly susceptible to malaria, they found that the mosquito-borne parasite produces a protein that binds to a particular type of sugar molecule in the placenta.

That discovery led to another: that same sugar molecule is also found in most cancers. This commonality is understandable, because both cancers and placentas grow rapidly, often pushing aside other tissues in the process.

The Copenhagen and Vancouver researchers realized that the sugar molecule could be a target for anti-cancer drugs, and that the malarial protein, called VAR2CSA, could provide the tool for carrying such drugs to tumours.

"Scientists have spent decades trying to find biochemical similarities between placenta tissue and cancer, but we just didn't have the technology to find it," said project leader Mads Daugaard, an assistant professor of urologic science at UBC and a senior research scientist at the Vancouver Prostate Centre, part of the Vancouver Coastal Health Research Institute. "When my colleagues discovered how malaria uses VAR2CSA to embed itself in the placenta, we immediately saw its potential to deliver cancer drugs in a precise, controlled way to tumours."

To test that theory, Daugaard and colleagues enlisted the expertise of John Babcook and his team at The Centre for Drug Research and Development (CDRD). They attached a novel toxin to VAR2CSA and treated hundreds of normal and cancer cell lines. The drug compound specifically targeted and killed more than 95 per cent of the cancer cell lines.

The drug was then tested on mice that were implanted with three types of human tumours. With non-Hodgkin's lymphoma, the treated mice's tumours were about a quarter the size of the tumours in the control group. With prostate cancer, the tumours completely disappeared in two of the six treated mice a month after receiving the first dose. With metastatic breast cancer, five out of six treated mice were cured from metastatic disease. The mice showed no adverse side-effects, and their organs were unharmed by the therapy. The results were published today in Cancer Cell.

"This is an extraordinary finding that paves the way for targeting sugar molecules in pediatric and adulthood human cancer, and our groups are vigorously pursuing this possibility together," said Poul Sorensen, a UBC professor of Pathology and

Laboratory Medicine and distinguished scientist with the BC Cancer Agency and co-senior investigator on the study.

"There is some irony that a disease as destructive as malaria might be exploited to treat another dreaded disease," said Ali Salanti, a professor of immunology and microbiology at the Centre for Medical Parasitology, at University of Copenhagen.

Two companies, Vancouver-based Kairos Therapeutics and Copenhagen-based VAR2 Pharmaceuticals, are developing the compound for clinical trials in humans, which will take another three to four years.

http://www.eurekalert.org/pub_releases/2015-10/uoe-sfl101315.php

Sitting for long periods not bad for health

There's no harm in sitting down, say researchers

New research from the University of Exeter and University College London has challenged claims that sitting for long periods increases the risk of an early death even if you are otherwise physically active.

The study, which is published in the International Journal of Epidemiology, followed more than 5000 participants for 16 years (making it one of the longest follow-up studies in this area of research) and found that sitting, either at home or at work, is not associated with an increased risk of dying.

These findings challenge previous research suggesting that the act of sitting itself causes harm even when people routinely walk a lot or do other exercise. Importantly, the findings contradict NHS recommendations which state that remaining seated for too long is bad for your health, regardless of how much exercise you do.

Dr Melvyn Hillsdon from Sport and Health Sciences at the University of Exeter said: "Policy makers should be cautious in recommending a reduction in the time spent sitting without also promoting increased physical activity".

"Our study overturns current thinking on the health risks of sitting and indicates that the problem lies in the absence of movement rather than the time spent sitting itself. Any stationary posture where energy expenditure is low may be detrimental to health, be it sitting or standing.

"The results cast doubt on the benefits of sit-stand work stations, which employers are increasingly providing to promote healthy working environments."

Lead author Dr Richard Pulsford from Sport and Health Sciences at the University of Exeter said: "Our findings suggest that reducing sitting time might not be quite as important for mortality risk as previously publicised and that encouraging people to be more active should still be a public health priority."

The study participants provided information on total sitting time and on four other specific types of sitting behaviour (sitting at work; during leisure time; while watching TV; and sitting during leisure time excluding TV) as well as details on daily walking and time spent engaged in moderate to vigorous physical activity. Age, gender, ethnicity, socioeconomic status, general health, smoking, alcohol consumption and diet were all taken into account. The study showed that over the 16 year follow-up period none of these five sitting measures influenced mortality risk.

Future work will consider whether long periods of sitting are associated with increased incidence of diseases such as heart disease and type II diabetes, and will investigate the biological mechanisms that underpin previously observed associations between sitting time and health outcomes.

The participants included 3720 men and 1412 women drawn from the Whitehall II study cohort which is supported by grants from the Medical Research Council, British Heart Foundation, Stroke Association, National Heart Lung and Blood Institute and the National Institute on Aging.

http://www.eurekalert.org/pub_releases/2015-10/e-aeo101315.php

Anticancer effects of drugs overestimated by as much as 45 percent in animal models

Poor study design threatens the validity of preclinical research

Badly designed studies may lead to the efficacy of drugs being overestimated and money being wasted on trials that prove fruitless, according to new a study from McGill University in Canada.

The findings, to be published in the journal eLife, highlight the importance of ensuring that preclinical research can be reproduced by other scientists. Reproducibility helps confirm the validity of results before clinical trials in humans go ahead.

"Only a fraction of drugs that show promise in animals end up proving safe and effective in humans," says lead researcher Dr Jonathan Kimmelman, who directs the STREAM (Studies in Translation, Ethics and Medicine) research group.

"An important reason is because studies in animals are often not well designed, and because positive results have a higher chance of being published. They end up skewing what we think we know about the potential of a drug."

The scientists looked at all the published animal studies of sunitinib, a cancer drug successfully used to treat advanced kidney cancer, a rare type of stomach cancer and rare tumours of the neuroendocrine system. They found evidence that studies that reported little or no anti-cancer effect were simply not published, leading anticancer effects of the drug to be overestimated by as much as 45%. The findings do not raise any concerns about the clinical use of sunitinib.

Few studies used practices like blinding or randomization, which help ensure personal expectations do not bias results. These practices, which are widely used

elsewhere in medical research, prevent the experimenter from knowing which animals receive the drug and which receive the control. Often it was not even clear how many animals had been tested because the sample size was not reported. The drug was tested against different types of cancer and all types tested showed statistically significant anti-cancer activity, a result which "strains credibility", according to Kimmelman. As well as over-estimating the effect of the drug on cancer-prone mice, the studies failed to observe the dose-dependent response to the drug that is known to occur in humans.

Finally, the studies failed to test the drug on a range of animal models, focusing instead on juvenile female mice with a compromised immune system. Malignancies tested in a wider range of animal types, such as mice that have spontaneously developed tumours, showed less extreme effect sizes.

"Preclinical research is plagued by poor design and reporting practices, exposing patients to harmful and inactive agents, wasting time in the lab and driving up the price of drugs," says Kimmelman.

This lack of rigour may help explain why only 5% of agents that show anticancer activity in preclinical development are eventually licensed, while in cardiovascular disease, for example, the rate is 20%.

The authors of the cancer study have suggestions for addressing the problems they uncovered in animal research and for tackling problems highlighted by others - such as in vitro tests using drug levels that would be unachievable in humans due to toxicity.

"Our findings provide compelling reasons for developing and implementing guidelines for the design and reporting of preclinical studies in cancer, similar to those already in use for stroke, epilepsy and cardiology," says Kimmelman.

http://bit.ly/1G9lS4m

Give Young Scientists the Keys to the Lab

Overly long apprenticeships for researchers often waste their most productive years

By Samuel L. Stanley, Jr. | October 13, 2015

When I think of the future of biomedical research, I think of my daughter. She is an MD/PhD student at Johns Hopkins University. By the time she graduates with both degrees she will be 30. She will have had four years of graduate school and superb scientific training (including published biomedical research as an undergraduate). But, according to data from the National Institutes of Health, she will have another 13 years to go before she will be competitive for the most common and substantial research grants the NIH offers.

Some of that time will be spent in clinical training but much of it will be in one or more postdoctoral stints, working as an apprentice to investigators who are senior to her. This prolonged training greatly shortens the independent careers of new researchers, and puts tremendous pressure on new faculty to be productive during the years when they are most likely to have the most extensive family demands. We need to find a way to fund these investigators earlier in their careers, when they are most innovative and productive.

Part of the answer lies in changing the culture of peer review. As it stands now, my daughter's first application will be at a disadvantage because she is a woman. According to Proceedings of the National Academy of Sciences, research shows that both men and women scientists will score an identical application higher when it comes from "John" than when it comes from "Jennifer." It is critically important that we scientists either do a better job educating ourselves about our inherent biases and their impact on our decision-making or find effective ways to blind reviewers to irrelevant data, like the gender, race or ethnicity of the applicant.

My daughter will also be at a disadvantage simply because she is a new applicant. There is a strong incumbency advantage—investigators under 45 achieve a lower funding rate than their older colleagues do. This advantage may be based on reviewers relying on the "track record" of accomplishment for older investigators. Also, those who are more established are likely to have a network of colleagues who know them and populate review panels. Again, it may be beneficial to blind reviewers to the applicant's identity, focusing reviews on the scientific merit of the proposal while putting less emphasis on the track record of the investigator.

Of course, the incumbency advantage may also speak to the inexperience of new investigators in preparing and submitting grant applications. That is where institutions and mentors must step to the plate, to provide better training, guidance and support for individuals submitting their first NIH Research Project Grant (R01) applications.

Young investigators like my daughter might benefit most from a recent proposal from the NIH to create an emeritus award for senior investigators who will pass their knowledge and their resources to a junior colleague. I think this approach can work, because I lived it.

My mentor at Washington University in Saint Louis—Joseph Davie, MD, PhD—transferred his NIH grant to me when he left academia for industry, giving me an R01 in my early 30s. This accelerated my career and helped me pursue my research goals, which I did for more than 22 years before transitioning to full-time administration. How wonderful it would be if my daughter, and many of our future scientists, could experience the same kind of rewarding career that Joe and I had.

The scientific community needs to work more broadly with funders of scientific research to develop ways to embrace and encourage younger scientists. It's not an easy task but it's a vital one because it's crucial that the best young scientists see a promising career ahead in scientific research, a major ingredient in our nation's economic preeminence.

It's time to make it happen.

http://www.eurekalert.org/pub_releases/2015-10/usmc-ssa101315.php

Study shows antioxidant use may promote spread of cancer

Cancer cells may benefit more from antioxidants than normal cells

DALLAS - A team of scientists at the Children's Research Institute at UT Southwestern (CRI) has made a discovery that suggests cancer cells benefit more from antioxidants than normal cells, raising concerns about the use of dietary antioxidants by patients with cancer. The studies were conducted in specialized mice that had been transplanted with melanoma cells from patients. Prior studies had shown that the metastasis of human melanoma cells in these mice is predictive of their metastasis in patients.

Metastasis, the process by which cancer cells disseminate from their primary site to other parts of the body, leads to the death of most cancer patients. The CRI team found that when antioxidants were administered to the mice, the cancer spread more quickly than in mice that did not get antioxidants. The study was published online today in Nature.

It has long been known that the spread of cancer cells from one part of the body to another is an inefficient process in which the vast majority of cancer cells that enter the blood fail to survive.

"We discovered that metastasizing melanoma cells experience very high levels of oxidative stress, which leads to the death of most metastasizing cells," said Dr. Sean Morrison, CRI Director and Mary McDermott Cook Chair in Pediatric Genetics at UT Southwestern Medical Center. "Administration of antioxidants to the mice allowed more of the metastasizing melanoma cells to survive, increasing metastatic disease burden."

"The idea that antioxidants are good for you has been so strong that there have been clinical trials done in which cancer patients were administered antioxidants," added Dr. Morrison, who is also a CPRIT Scholar in Cancer Research and a Howard Hughes Medical Institute Investigator. "Some of those trials had to be stopped because the patients getting the antioxidants were dying faster. Our data suggest the reason for this: cancer cells benefit more from antioxidants than normal cells do."

Healthy people who do not have cancer may very well benefit from antioxidants that can help reduce damage from highly reactive oxidative molecules generated by normal metabolism. While the study's results have not yet been tested in people, they raise the possibility that cancer should be treated with pro-oxidants and that cancer patients should not supplement their diet with large doses of antioxidants.

"This finding also opens up the possibility that when treating cancer, we should test whether increasing oxidative stress through the use of pro-oxidants would prevent metastasis," said Dr. Morrison. "One potential approach is to target the folate pathway that melanoma cells use to survive oxidative stress, which would increase the level of oxidative stress in the cancer cells."

Other CRI researchers involved in the research were first author, Dr. Elena Piskounova; Dr. Michalis Agathocleous; Dr. Malea M. Murphy; and Dr. Ralph DeBerardinis, Associate Professor

of Pediatrics and in the Eugene McDermott Center for Human Growth and Development at UT Southwestern, who also holds the Joel B. Steinberg, M.D. Chair in Pediatrics and is a Sowell Family Scholar in Medical Research. The work was supported by the Howard Hughes Medical Institute, the Cancer and Prevention Research Institute of Texas, and donors to the Children's Medical Center Foundation.

http://www.eurekalert.org/pub_releases/2015-10/miot-tso101415.php

To save on weight, a detour to the moon is the best route to Mars

For a piloted mission to Mars, fueling up on the moon could streamline cargo by 68 percent

Launching humans to Mars may not require a full tank of gas: A new MIT study suggests that a Martian mission may lighten its launch load considerably by refueling on the moon.

Previous studies have suggested that lunar soil and water ice in certain craters of the moon may be mined and converted to fuel. Assuming that such technologies are established at the time of a mission to Mars, the MIT group has found that taking a detour to the moon to refuel would reduce the mass of a mission upon launch by 68 percent.

The group developed a model to determine the best route to Mars, assuming the availability of resources and fuel-generating infrastructure on the moon. Based on their calculations, they determined the optimal route to Mars, in order to minimize the mass that would have to be launched from Earth -- often a major cost driver in space exploration missions.

They found the most mass-efficient path involves launching a crew from Earth with just enough fuel to get into orbit around the Earth. A fuel-producing plant on the surface of the moon would then launch tankers of fuel into space, where they would enter gravitational orbit. The tankers would eventually be picked up by the Mars-bound crew, which would then head to a nearby fueling station to gas up before ultimately heading to Mars.

Olivier de Weck, a professor of aeronautics and astronautics and of engineering systems at MIT, says the plan deviates from NASA's more direct "carry-along" route.

"This is completely against the established common wisdom of how to go to Mars, which is a straight shot to Mars, carry everything with you," de Weck says. "The idea of taking a detour into the lunar system ... it's very unintuitive. But from an optimal network and big-picture view, this could be very affordable in the long term, because you don't have to ship everything from Earth."

The results, which are based on the PhD thesis of Takuto Ishimatsu, now a postdoc at MIT, are published in the Journal of Spacecraft and Rockets.

A faraway strategy

In the past, space exploration programs have adopted two main strategies in supplying mission crews with resources: a carry-along approach, where all vehicles and resources travel with the crew at all times -- as on the Apollo missions to the moon -- and a "resupply strategy," in which resources are replenished regularly, such as by spaceflights to the International Space Station.

However, as humans explore beyond Earth's orbit, such strategies may not be sustainable, as de Weck and Ishimatsu write: "As budgets are constrained and destinations are far away from home, a well-planned logistics strategy becomes imperative."

The team proposes that missions to Mars and other distant destinations may benefit from a supply strategy that hinges on "in-situ resource utilization" -- the idea that resources such as fuel, and provisions such as water and oxygen, may be produced and collected along the route of space exploration. Materials produced in space would replace those that would otherwise be transported from Earth.

For example, water ice -- which could potentially be mined and processed into rocket fuel -- has been found on both Mars and the moon.

"There's a pretty high degree of confidence that these resources are available," de Weck says. "Assuming you can extract these resources, what do you do with it? Almost nobody has looked at that question."

Building a network in space

To see whether fuel resources and infrastructure in space would benefit manned missions to Mars, Ishimatsu developed a network flow model to explore various routes to Mars -- ranging from a direct carry-along flight to a series of refueling pit stops along the way. The objective of the model was to minimize the mass that would be launched from Earth, even when including the mass of a fuel-producing plant, and spares that would need to be pre-deployed.

The approach models the movement of cargo and commodities, such as fuel, in a supply chain network in space. Ishimatsu developed a new mathematical model that improves on a conventional model for routing vehicles. He adapted the model for the more complex scenario of long-term missions in space -- taking into account constraints specific to space travel.

The model assumes a future scenario in which fuel can be processed on, and transported from, the moon to rendezvous points in space. Likewise, the model assumes that fuel depots can be located at certain gravitationally bound locations in space, called Lagrange points. Given a mission objective, such as a set of weight restrictions, the model identifies the best route in the supply network, while also satisfying the constraints of basic physics.

Ishimatsu says the research demonstrates the importance of establishing a resource-producing infrastructure in space. He emphasizes that such infrastructure may not be necessary for a first trip to Mars. But a resource network in space would enable humans to make the journey repeatedly in a sustainable way.

"Our ultimate goal is to colonize Mars and to establish a permanent, self-sustainable human presence there," Ishimatsu says. "However, equally importantly, I believe that we need to 'pave a road' in space so that we can travel between planetary bodies in an affordable way."

"The optimization suggests that the moon could play a major role in getting us to Mars repeatedly and sustainably," de Weck adds. "People have hinted at that before, but we think this is the first definitive paper that shows mathematically why that's the right answer."

http://www.bbc.com/news/science-environment-34531861

Fossil teeth place humans in Asia '20,000 years early'

By Paul Rincon Science editor, BBC News website

Fossil finds from China have shaken up the traditional narrative of humankind's dispersal from Africa.

Scientists working in Daoxian, south China, have discovered teeth belonging to modern humans that date to at least 80,000 years ago. This is 20,000 years earlier than the widely accepted "Out of Africa" migration that led to the successful peopling of the globe by our species.

Details of the work are outlined in the journal Nature.

The 47 human teeth were found sealed in a cave, beneath 80,000-year-old stalagmites **S Xing, X-J Wu**

Several lines of evidence - including genetics and archaeology - support a dispersal of our species from Africa 60,000 years ago.

Early modern humans living in the horn of Africa are thought to have crossed the Red Sea via the Bab el Mandeb straits, taking advantage of low water levels.

All non-African people alive today are thought to derive from this diaspora. Now, excavations at Fuyan Cave in Daoxian have unearthed a trove of 47 human teeth.

Ancient diaspora

"It was very clear to us that these teeth belonged to modern humans [from their morphology]. What was a surprise was the date," Dr María Martinón-Torres, from University College London (UCL), told BBC News.

"All the fossils have been sealed in a calcitic floor, which is like a gravestone, sealing them off. So the teeth have to be older than that layer. Above that are stalagmites that have been dated using uranium series to 80,000 years.

This means that everything below those stalagmites must be older than 80,000 years old; the human teeth could be as old as 125,000 years, according to the researchers.

Modern humans reached the Levant 125,000 years ago, but this migration has been regarded as a failed foray outside Africa **Science Photo Library**

In addition, the animal fossils found with the human teeth are typical of the Late Pleistocene - the same period indicated by the radioactive dating evidence.

Some fossils of modern humans that predate the Out of Africa migration are already known, from the Skhul and Qafzeh caves in Israel.

But these have been regarded as part of a failed early dispersal of modern humans who probably went extinct.

However, the discovery of unequivocally modern fossils in China clouds the picture. "Some researchers have proposed earlier dispersals in the past," said Dr Martinón-Torres.

"We really have to understand the fate of this migration. We need to find out whether it failed and they went extinct or they really did contribute to later people.

"Maybe we really are descendents of the dispersal 60,000 years ago - but we need to re-think our models. Maybe there was more than one Out of Africa migration."

'Game-changer'

Prof Chris Stringer, from London's Natural History Museum said the new study was "a game-changer" in the debate about the spread of modern humans.

"Many workers (often including me) have argued that the early dispersal of modern humans from Africa into the Levant recorded by the fossils from Skhul and Qafzeh at about 120,000 years ago was essentially a failed dispersal which went little or no further than Israel."

"However, the large sample of teeth from Daoxian seem unquestionably modern in their size and morphology, and they look to be well-dated by uranium-thorium methods to at least 80,000 years. At first sight this seems to be consistent with an early dispersal across southern Asia by a population resembling those known from Skhul and Qafzeh.

"But the Daoxian fossils resemble recent human teeth much more than they look like those from Skhul and Qafzeh, which retain more primitive traits. So either there must have been rapid evolution of the dentitions of a Skhul-Qafzeh type population in Asia by about 80,000 years, or the Daoxian teeth represent a hitherto-unsuspected early and separate dispersal of more modern-looking humans."

Dr Pontus Skoglund, from the department of genetics at Harvard Medical School, told BBC News: "The genetic evidence we have puts strong constraints on some aspects of human history, but less so on the timing of the out of Africa event. Most genetic reconstructions based on modern data relies on assumptions on the mutation rate, for which there are still some real uncertainties.

"In terms of direct genetic evidence, we already have a 45,000 year-old genome from Siberia (Ust Ishim) and a ~40,000 year old individual from Europe (Oase) that are consistent with being from now-mostly-extinct lineages. "

"The conclusion is perhaps that the genetics does allow an 80,000 year old East Asian population to contribute some ancestry to present-day people, but I think not very much. It is a very interesting discovery that is hard to fit in our current thinking, but not impossible. We are just starting to cope with this data point."

Dr Martinón-Torres said the study could also shed light on why it took *Homo sapiens* another 40,000 years to settle Europe.

Perhaps the presence of the Neanderthals kept our species out of westernmost Eurasia until our evolutionary cousins started to dwindle in number.

However, it's also possible that modern humans - who started out as a tropical species - were not as well-conditioned as the Neanderthals for the icy climate in Europe.

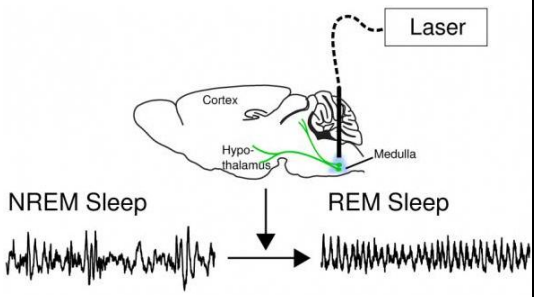
She noted that while modern humans occupied the warmer south of China 80,000 years ago, the colder regions of central and northern China appear to be settled by more primitive human groups who may have been Asian relatives of the Neanderthals.

http://www.eurekalert.org/pub_releases/2015-10/uoc--rfn101415.php

Researchers find neural switch that turns dreams on and off

Activating small group of neurons in medulla causes rapid transition to REM sleep

At the flip of a switch, University of California, Berkeley, neuroscientists can send a sleeping mouse into dreamland. The researchers inserted an optogenetic switch into a group of nerve cells located in the ancient part of the brain called the medulla, allowing them to activate or inactivate the neurons with laser light.



When a laser triggers an optogenetic switch in neurons in the medulla of a sleeping mouse, the animal goes from non-REM sleep (NREM) into REM or dream sleep. The axons of these neurons (green) reach into distant parts of the primitive brain, such as the hypothalamus, broadly affecting brain function. **Franz Weber/UC Berkeley**

When the neurons were activated, sleeping mice entered REM sleep within seconds. REM sleep, characterized by rapid eye movements, is the dream state in mammals accompanied by activation of the cortex and total paralysis of the skeletal muscles, presumably so that we don't act out the dreams flashing through our mind. Inactivating the neurons reduced or even eliminated a mouse's ability to enter REM sleep.

"People used to think that this region of the medulla was only involved in the paralysis of skeletal muscles during REM sleep," said lead author Yang Dan, a UC Berkeley professor of molecular and cell biology and a Howard Hughes Medical Institute Investigator. "What we showed is that these neurons triggered all aspects of REM sleep, including muscle paralysis and the typical cortical activation that makes the brain look more awake than in non-REM sleep."

While other types of neurons in the brainstem and hypothalamus have been shown to influence REM sleep, Dan said, "Because of the strong induction of REM sleep - in 94 percent of the recorded trials our mice entered REM sleep within seconds of activating the neurons - we think this might be a critical node of a relatively small network that makes the decision whether you go into dream sleep or not."

The UC Berkeley team reported their results in the Oct. 15 print issue of the British journal Nature, and the paper was posted online Oct. 7.

The discovery will not only help researchers better understand the complex control of sleep and dreaming in the brain, the researchers said, but will allow scientists to stop and start dreaming at will in mice to learn why we dream.

"Many psychiatric disorders, especially mood disorders, are correlated with changes in REM sleep, and some widely used drugs affect REM sleep, so it seems to be a sensitive indicator of mental and emotional health," said first author Franz Weber, a UC Berkeley postdoctoral fellow. "We are hoping that studying the sleep circuit might lead us to new insights into these disorders as well as neurological diseases that affect sleep, like Parkinson's and Alzheimer's diseases."

Eating and dreaming

The researchers also found that activating these brain cells while the mice were awake had no effect on wakefulness, but did make them eat more. In normal mice, these neurons - a subset of nerve cells that release the neurotransmitter gamma-amino butyric acid (GABA), and so are called GABAergic neurons - are most active during waking periods when the mice are eating or grooming, two highly pleasurable activities.

Dan suspects that these GABAergic neurons in the medulla have the opposite effect of stress neurons, such as the noradrenergic neurons in the pons, another ancient part of the brain. Noradrenergic neurons release the transmitter noradrenalin, a cousin of adrenalin.

"Other people have found that noradrenergic neurons, which are active when you are running, shut down when eating or grooming. So it seems like when you are relaxed and enjoying yourself, the noradrenergic neurons switch off and these GABAergic neurons in the medulla turn on," she said.

The GABAergic neurons project from the ventral part of the medulla, which sits at the top of the spinal cord, into many regions of the brainstem and hypothalamus, and thus are able to affect many bodily functions. These regions - more primitive than the brain's cortex, the center of thinking and reasoning - are the seat of emotions and many innate behaviors as well as the control centers for muscles and automatic functions such as breathing.

Optical brain state switching

Dan, Weber and their colleagues chose a powerful technique called optogenetics to study these REM-related GABAergic neurons in the medulla. The technique involves inserting a light-sensitive ion channel into specific types of neurons by means of a virus. To target the virus to GABAergic neurons, the researchers used a genetically engineered mouse line that expresses a marker protein in these specific neurons only. Once present, the ion channel can turn on the activity of neurons when stimulated by laser light through an optical fiber inserted in the brain. Alternatively, inserting an inhibitory ion pump into the GABAergic neurons allowed the researchers to turn off the activity of these neurons through laser stimulation.

Using this genetically engineered strain of mice, the researchers mapped the activity of these neurons in the medulla and then recorded how activating or inactivating the neurons for brief periods affected sleep and waking behavior.

They also used a drug to inactivate the same set of neurons and found a reduction of REM sleep, though not as immediate and lasting for a longer period of time, since the drug required about half an hour to take effect and wore off slowly.

They also inserted the light-sensitive ion channels into a different set of neurons in the medulla: glutamatergic neurons, which release the neurotransmitter glutamate. Activating these neurons immediately awakened the animals, the opposite effect of activating the GABAergic neurons.

Dan is continuing her studies of the neurons that affect not only REM sleep, but also non-REM sleep.

The work was supported by Weber's postdoctoral fellowships from the European Molecular Biology Organization and the Human Frontier Science Program. Other authors were Shinjae Chung and Min Xu of UC Berkeley and Kevin Beier and Liqun Luo of Stanford University.

http://www.eurekalert.org/pub_releases/2015-10/e-jrp101515.php

Journal Resuscitation publishes updated European Resuscitation Council guidelines

2015 European Resuscitation Council guidelines now available free to download

Amsterdam - Elsevier, a world-leading provider of scientific, technical and medical information products and services, today announced the publication of the 2015 European Resuscitation Council (ERC) Guidelines, in the latest issue of journal Resuscitation. These guidelines are based on an extensive international review of all the science supporting cardiopulmonary resuscitation (CPR). The 2015 International Consensus on CPR Science, is also published in Resuscitation today. This year also marks the 55th anniversary since CPR was first developed.

The updated ERC Guidelines include detailed advice for healthcare professionals on how to treat cardiac arrest and how to continue to treat the patient after the heart has been restarted. The ERC Guidelines 2015 include detailed instructions to members of the public who may be in a position to save a life by providing bystander CPR to a victim of cardiac arrest. The 2015 International Consensus on CPR Science is a valuable resource for CPR researchers as well as clinicians.

Professor Jerry Nolan, Editor-in-Chief of Resuscitation, said, "These guidelines are derived from a comprehensive review of CPR science that was undertaken by experts from around the world. They provide recommendations on best practice for resuscitation across the whole patient pathway." The last ERC Guidelines were published in 2010; in the 2015 Guidelines, changes have been made only if supported by scientific evidence or if the change would simplify the resuscitation process.

According to the 2015 ERC Guidelines, if more people in Europe were trained to provide CPR it could be possible to save an additional 100.000 lives. Therefore it is of major importance that health media in the European countries make both lay people and healthcare professionals aware of the new 2015 ERC Guidelines.

Issue details: Resuscitation, Vol 95 (October 2015) published by Elsevier

Download the 2015 ERC guidelines and the International Consensus on CPR Science for free: http://www.resuscitationjournal.com/current

Background

Throughout Europe, each year, about 500,000 people have an out-of-hospital sudden cardiac arrest. Currently, less than 10% of these survive to leave hospital. If a bystander provides CPR, the chance of a cardiac arrest victim surviving is increased by about 2-3 times. Currently, in Europe CPR is given by a bystander in only about 25-30% of cardiac arrests. Standard CPR includes compressing the chest and giving mouth-to-mouth rescue breathing.

The ERC Guidelines 2015 emphasize that if a bystander sees someone collapse suddenly, and if they are unresponsive and not breathing normally, they should first alert the emergency services and then start chest compressions by pushing down at least 5 cm in the middle of the chest at a rate of 100-120 compressions per minute. If the bystander is trained in standard CPR, and they are confident and willing to provide rescue breathing, after giving 30 chest compressions they should give two rescue breaths followed by another 30 chest compressions. CPR is continued with this compression to breathing ratio of 30:2. The bystander who is untrained in CPR should at least give chest compressions continuously ('press hard and fast') until the ambulance arrives: 'any CPR is better than no CPR'. The ambulance dispatcher plays an important role in the early diagnosis of cardiac arrest and the provision of dispatcher-assisted CPR (also known as telephone CPR). The ERC Guidelines indicate that if an ambulance dispatcher gives telephone advice to a bystander on how to do CPR, they should be told to do compression-only CPR.

In many cases of cardiac arrest, the heart can be restarted with an electric shock (defibrillation). Defibrillation within 3-5 minutes of collapse can produce survival rates as high as 50-70%. Early defibrillation can be achieved by bystanders using public access automated external defibrillators (AEDs). The ERC Guidelines 2015 highlight the critical importance of the interactions between the ambulance dispatcher, the bystander who provides CPR and the timely deployment of an AED. An effective, coordinated community response that draws these elements together is key to improving survival from cardiac arrest.

The ERC Guidelines 2015 also provide updated guidance to healthcare professionals on how to optimise the treatment of a person whose heart has been restarted after cardiac arrest. In many cases this includes early access to a 'cardiac arrest centre' to enable treatment of blocked coronary arteries and ongoing support of vital organs and close control of body temperature in an intensive care unit (ICU). There is emphasis on the frequent need for longer treatment periods in the ICU.

Issue details: Resuscitation, Vol 95 (October 2015) published by Elsevier
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http://www.bbc.com/news/science-environment-34540193

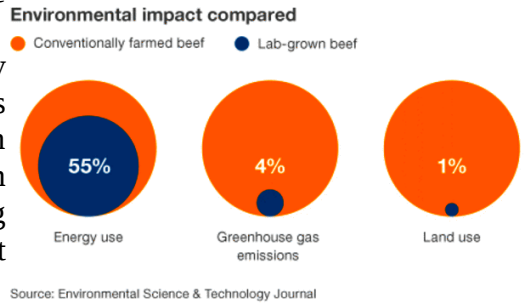
Team wants to sell lab grown meat in five years

The Dutch team who have grown the world's first burger in a lab say they hope to have a product on sale in five years.

By Pallab Ghosh Science correspondent, BBC News

Researchers are to set up a company to look at making the burger tastier and cheaper. The team had a prototype cooked and eaten in London two years ago that cost £215,000 to make. The head of the new firm set out his plans to BBC News ahead of a symposium on developing the technology.

Peter Verstrate said: "I feel extremely excited about the prospect of this product being on sale. And I am confident that when it is offered as an alternative to meat that increasing numbers of people will find it hard not to buy our product for ethical reasons".



An independent study found that lab-grown beef uses 45% less energy than the average global representative figure for farming cattle. It also produces 96% fewer greenhouse gas emissions and requires 99% less land.

The lab-grown burger was developed by Prof Mark Post at his laboratory in Maastricht University, The Netherlands. "I am confident that we will have it on the market in five years," he said. He explained it would be available as an exclusive product to order to begin with but would be on supermarket shelves once a demand had been established and the price comes down.

The burger is made from stem-cells: the templates from which specialised tissue such as nerve or skin cells develop. Most researchers working in this area are trying to grow human tissue for transplantation to replace worn-out or diseased muscle, nerve cells or cartilage. Prof Post, however, used them to grow muscle and fat for his burger. The motivation for the research is to find ways of keeping up with the growing demand for meat. Traditional farming methods will need to use more energy, water and land - and the consequent increase in greenhouse gas emission will be substantial.

The process starts with stem cells being extracted from cow muscle tissue. In the laboratory, these are cultured with nutrients and growth-promoting chemicals to help them develop and multiply. Three weeks later, there are more than a million stem cells, which are put into smaller dishes where they coalesce into small strips of muscle about a centimetre long and a few millimetres thick.

The strips are then painstaking layered together, coloured and mixed with fat.

The resulting burger was cooked and eaten at a news conference in London two years ago. One food expert said it was "close to meat, but not that juicy" and another said it tasted like a real burger.

Mr Verstrate told BBC News that it was a proof of principle but not yet a finished product. "It consisted of protein, muscle fibre. But meat is much more than that it is blood, its fat its connective tissue, all of which adds to the taste and texture".

"If you want to mimic meat you have to make all those things too - and you can use tissue engineering technologies - but we hadn't done that at the time".

The company which he has formed with Prof Post and Maastricht University, called Mosa Meat, plans to develop lab-grown minced meat that is as tasty as the real thing and costs the same.

Prof Post and his team have made progress in the past two years - but to develop a commercial product in five years he decided he had to ramp up the research.

Mosa Meat will employ up to 25 scientists, lab technicians and managers. One of the key objectives will be to find ways of mass producing the meat.

The researchers will also investigate ways of making chops and steaks using 3-D printing technologies - but that is likely to take longer to commercialise.

http://www.bbc.com/news/health-34540363

Immune clue to preventing schizophrenia

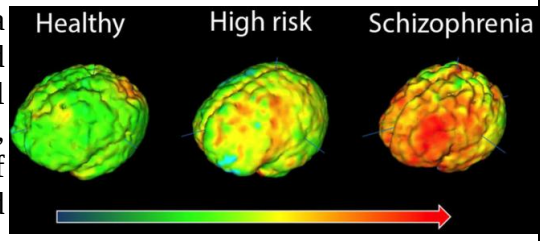
It may be possible to prevent schizophrenia by calming the brain's immune system, say scientists.

By James Gallagher Health editor, BBC News website

Brain scans found an overactive immune system in patients as well as in those at high risk of schizophrenia. The UK Medical Research Council team wants to test anti-inflammatory drugs to treat or even prevent the disease. Other experts in the field said the study, in the American Journal of Psychiatry, was "important" and furthered understanding of the illness.

There has been mounting evidence that the immune system and inflammation play a key role in schizophrenia and other psychiatric conditions. The researchers

analysed microglia, which are like the brain's own gardeners weeding out infection but also "pruning" unwanted connections between brain cells. A chemical dye which sticks to microglia was injected into 56 people to record their microglia activity. The highest level was found in patients with the condition, but those deemed at high risk of developing schizophrenia also showed heightened activity levels.



Brain scans discovered higher activity levels in part of the brain's immune system in schizophrenia patients than in healthy volunteers **Image copyright MRC**

Dr Oliver Howes, the head of the psychiatric imaging group at the MRC Clinical Sciences Centre, told the BBC News website: "This is a real step forward in understanding. "For the first time we have evidence that there is over-activity even before full onset of the illness. "If we could reduce activity [before full-blown illness] then we might be able to prevent the illness - that needs to be tested, but is one key implication [of the research]."

He thinks the microglia become like a gardener too keen with the shears and sever the wrong connections in the brain leaving it wired incorrectly. "You can see how that would lead to patients making unusual connections between what is happening around them or mistaking thoughts as voices outside their head and causing the symptoms we see in the illness," Dr Howes added.

Treatments

Some small trials have suggested that anti-inflammatory drugs may help patients when they have been given alongside traditional medication. However, further studies are now needed including on anti-inflammatory drugs that target only the microglia rather than those, such as Ibuprofen, that have a wider effect on the body. Dr Howes advised patients not to self-prescribe the drugs and added that any decisions about medication should be made with a doctor. It is not yet clear why some people have overly active microglia.

Analysis of patients' DNA - their blueprint of life - has implicated genes that control the immune system. It suggests some patients are predisposed to having a more sensitive immune system, but events later in life such as times of high stress have also been implicated.

The head of psychiatry at the University of Edinburgh, Prof Stephen Lawrie, commented: "This is an important paper, which both confirms and extends previous findings, in a carefully controlled and state-of the-art study." He said the findings "suggests the possible amelioration or even prevention of one of the worst illnesses affecting mankind" through drugs to tame the immune system in the brain.

http://www.bbc.com/news/uk-england-hampshire-34547263

Britain's oldest person Gladys Hooper has hip op at 112

A 112-year-old woman from the Isle of Wight is believed to be the oldest person in the world to have had a hip replacement.

Gladys Hooper, from Ryde, needed emergency surgery after fracturing her hip when she fell at home. Orthopaedic surgeon Jason Millington said: "She's an amazing lady, to my knowledge she's the oldest person documented to have had this procedure." Mrs Hooper is recovering at the island's St Mary's Hospital.

The hospital said notwithstanding her age it was right to spend £6,000 on the operation to fit the ceramic hip.

Mr Millington said: "This was emergency surgery, it's not based on age. "My philosophy is never too old to operate, just too unwell, and in Mrs Hooper's case she was certainly well enough. "If the benefits of the surgery outweigh the risk then it's a pretty easy decision and you operate. "She deserves treatment as much as anyone else."

Following the operation Mrs Hooper said she felt "somewhere near 80" in age.

This was an emergency operation to replace half of the right hip joint, after the patient's hip was fractured in a fall. Instead of a total hip replacement, only the ball portion of the hip was replaced - not the socket.

Hip replacements are a common procedure, usually carried out in older people between 60 and 80 because of wear and tear or damage to the hip joint. Patients over 100 years old are unusual, but their number is increasing because people are living longer. The risks of undergoing a general anaesthetic at that age can be risky. But there are other options - in this case a spinal anaesthetic was used.

The challenge now for Mrs Hooper is to get back on her feet and use her new hip - a process which can take four to six weeks for even the most mobile patients.

http://www.eurekalert.org/pub_releases/2015-10/ciot-tdt101515.php

Taking dinosaur temperatures with eggshells

Insight into how dinosaurs may have regulated their internal heat

Researchers know dinosaurs once ruled the earth, but they know very little about how these animals performed the basic task of balancing their energy intake and output--how their metabolisms worked. Now, a team of Caltech researchers that has measured the body temperatures of a wide range of dinosaurs has provided insight into how the animals may have regulated their internal heat.

The study was led by John Eiler, the Robert P. Sharp Professor of Geology and professor of geochemistry, and Rob Eagle, a former Caltech postdoctoral scholar

now at UCLA. A paper describing the research appears in the October 13 issue of the journal Nature Communications.

The current study examined eggshells from the sauropods, a group that includes some of the biggest dinosaurs ever to live, called Titanosaurs, as well as eggshells of birdlike and approximately human-sized oviraptorid dinosaurs. The eggshells were analyzed to determine the extent to which carbon-13 and oxygen-18--rare, naturally occurring isotopes (variant forms of elements that differ in number of neutrons)--group together in the mineral structure. This "clumping" of rare isotopes previously has been shown to depend on mineral growth temperature. The eggshell data were compared with the results of a previous study by this same group that used similar techniques to examine the growth temperatures of the sauropod dinosaurs, including the giraffe-like Giraffatitan and a giant herbivore known as Camarasaurus.

The isotopic composition of the eggshells showed that smaller oviraptorid dinosaurs had body temperatures of 32 degrees Celsius--decidedly cooler than modern mammals and birds. The body temperatures of the larger Titanosaur dinosaurs were 38 degrees Celsius, indistinguishable from a previous finding for Giraffatitan teeth and similar to modern mammals. This finding--that larger dinosaurs maintained body temperatures like ours whereas smaller ones more closely resembled modern reptiles--has implications for our understanding of dinosaur physiology.

Modern mammals are described as warm blooded if they regulate their own temperature, as if tweaking an internal thermostat. In a process called endothermy, warm-blooded mammals utilize the heat generated by their own internal functions instead of drawing ambient heat from the environment, which is what a cold-blooded snake or lizard does by basking in the sun. Endothermy is relatively similar across many different sizes of mammals, from mice to humans to whales.

"Measuring cooler temperatures in small dinosaurs is the first evidence to suggest that at least some of them had lower basal metabolisms than most modern mammals and birds, and therefore the emergence of modern mechanisms of endothermy hadn't occurred in these dinosaurs," Eiler says.

The picture is not so clear for the larger dinosaurs that were studied. Although Eiler and his colleagues found that they had warm body temperatures similar to modern mammals, it is not known if the animals actually had endothermic metabolisms or if they were warm simply because of their enormous sizes--a phenomenon known as gigantothermy. Gigantotherms have small surface areas relative to their large volumes and thus have less area through which they can lose heat. Therefore, the heat is trapped internally. "If you weigh 80 tons, your problem is not staying warm--it's trying not to burst into flames," Eiler says.

The wide range of warm temperatures discovered among the various dinosaur species examined in the study suggests that "either they had a range of different metabolic strategies, or they all had low basal metabolisms, and the large ones were only warm due to gigantothermy," Eiler says.

The technique used to determine these animal body temperatures was first conceived and used by Eiler's group in 2011 on dinosaur tooth fossils and is related to methods they previously developed for nonbiological minerals and molecules. The method, called the clumped-isotope technique, relies on measurements of rare isotopes in bioapatite, or biologically grown calcium carbonate, a mineral present in bones, teeth, eggshells, and other fossils. In 2006, Eiler's lab quantified the degree to which carbon-13 and carbon-18 clump together to varying degrees in a biomineral, depending on the temperature at the time the mineral formed; this relationship subsequently was examined for many mineral types by Eiler's group at Caltech and at other laboratories.

"There's this cool idea that if I had a fossil skeleton, I could map the body temperature of the entire creature and come up with a physiological model of how it redistributed heat within its body," Eiler says. "There's no reason you couldn't do that, except that bone isn't very well preserved."

The team's next step is to compare fossils from the same species across stages of maturation. "It may be that some dinosaurs have a different metabolic strategy at different phases of life," Eiler says.

http://www.eurekalert.org/pub_releases/2015-10/uot-ngb101615.php

Nicotine gives brain more codeine relief, risk of addiction

In rat models, nicotine use over time increases the speed that codeine is converted into morphine within the brain

According to new research in rat models, nicotine use over time increases the speed that codeine is converted into morphine within the brain, by increasing the amount of a specific enzyme. It appears smokers' brains are being primed for a bigger buzz from this common pain killer - which could put them at a higher risk for addiction, and possibly even overdose.

"We've known for some time that codeine was metabolized in the liver, but we've now discovered that this is also happening within the brain itself," says University of Toronto pharmacology, toxicology, and psychiatry professor Rachel Tyndale, who is also senior scientist in the Campbell Family Mental Health Research Institute at the Centre for Addiction and Mental Health (CAMH). "Chronic nicotine use, or smoking, increases the amount of an enzyme that converts codeine into morphine within the brain, increasing pain relief. This may also make you more prone to addiction as the faster a drug gives you a high, the easier it is for you to learn the behavior and become addicted."

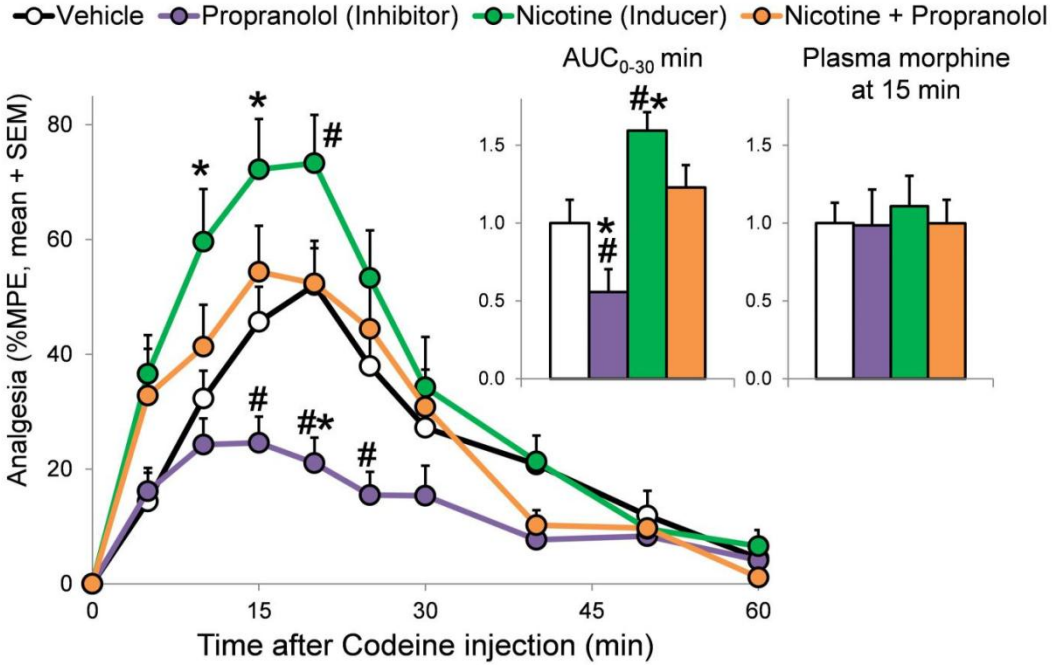


Fig 2 Induction of brain CYP2D by nicotine increased **CODEINE**-induced analgesia, both %MPE and AUC, which was blocked by inhibiting brain CYP2D with propranolol. Inhibition of brain CYP2D with propranolol decreased analgesia. At 15 minutes (peak analgesia), there were no differences between plasma morphine levels after codeine administration. A within-animal study design was used, n=12/group; *p<0.05, compared with vehicle, and #p<0.05, compared with the nicotine + propranolol. Repeated-measures ANOVA with a Bonferroni *post hoc* test[6].

These findings, published earlier this year in the peer-reviewed journal Neuropsychopharmacology, are part a new way of seeing the brain's role when it comes to drugs and toxins. Instead of a passive target with receptors idly waiting for drugs, Tyndale has found that the brain is actually playing a much more active role than was previously thought. Enzymes in the brain are busy breaking down - or ramping up - the effect of drugs and other substances. Understanding these enzymes - and our genetic variation affecting our brain's metabolism - could help explain why people react differently to drugs and toxins, and even why certain people are more susceptible to complex diseases like Parkinson's.

"This is opening up a whole new area of research and potentially a substantial source of variation between people in their response to drugs and toxins acting on the brain," says Tyndale. "We're starting to see patterns and relationships, like the nicotine and codeine connection. This is also of interest in drug development as we might be able to create drugs that are only activated once they get to the brain."

For this study, Tyndale, and her graduate student Douglas McMillan administered codeine to rats and measured their pain relief and levels of codeine and morphine. One group was given nicotine for seven days prior to the codeine. Another group received propranolol, which is known to inhibit the enzyme and block the activation of codeine. A third group received both nicotine and propranolol and a fourth was given neither, as a control. Tyndale found substantially more morphine and greater pain relief in the rats that had been given nicotine. Those who also received the inhibitor (propranolol) had less morphine in the brain and experienced less pain relief. The group that received the inhibitor and not the nicotine had the lowest levels of both brain morphine and pain relief. Despite this variation within the brain, the levels of morphine in the blood remained around the same for all groups - showing that it was variation in the activity of the enzyme within the brain, and not within the liver, that determined the effect of codeine on pain relief. People with more of this enzyme in their brain, whether due to genetic factors, smoking, vaping or other nicotine use, might be getting more pain relief but could be at greater risk of codeine dependence.

"This work could explain a lot of the mysteries when it comes to why people react so differently to different drugs, even when their blood levels seem to be similar," says Dr. Julia Stingl, a professor of translational pharmacology at the University of Bonn Medical School and a clinical pharmacologist who treats patients with depression and additions. "Understanding the effects of smoking on metabolizing enzymes in the brain could have an extreme impact on clinical practice."

Variation in how people react to drugs has long puzzled clinicians and researchers. For example, certain people do not have any of the enzyme that converts codeine into morphine. For a time health care workers believed these individuals were abusing their medication - continually asking for more - when in fact they were not getting any pain relief.

Tyndale's research into how the brain metabolizes drugs and toxins could expand our understanding of a host of unexplained associations. For example, researchers have found that smokers have a lower risk of developing Parkinson's disease compared to their non-smoking counterparts. Tyndale has found that the same enzyme that converts codeine into morphine - the one increased with nicotine intake - is also able to break down a toxin that causes a Parkinsonian symptom in rats. She's currently doing more research into this link.

Another puzzle is a genetic variation in a different enzyme that, while tied to nicotine addiction, does not alter nicotine levels in the blood. Research in animal models by Tyndale, graduate student Kristine Garcia and U of T pharmacology

professor and CAMH senior scientist Anh Dzung Lê - which was also published this year in the journal Neuropsychopharmacology - found that the variation in activity within the brain indeed leads to changes in brain nicotine levels. As seen with humans, those with low levels of this brain enzyme have more active nicotine in their brains and are at greater risk of addiction to nicotine. As it turns out, the same enzyme is at play in converting a common herbicide used in agriculture into its toxic form.

Viewing the brain not just as a passive array of receptors for drugs, but as an active metabolizer, stands to reveal important insights into how we react differently to a range of medications, drugs, toxins and even our susceptibility to certain diseases. Tyndale is currently expanding her research into variation in human brain enzyme activity, using a variety of experimental and imaging approaches.

http://www.eurekalert.org/pub_releases/2015-10/uol-ctp101515.php

Camels test positive for respiratory virus in Kenya

Nearly half of camels in parts of Kenya have been infected by the MERS virus

A new study has found that nearly half of camels in parts of Kenya have been infected by the virus that causes Middle East Respiratory Syndrome (MERS) and calls for further research into the role they might play in the transmission of this emerging disease to humans.

MERS was first identified in Saudi Arabia in 2012 and there is currently no vaccine or specific treatment available. To date, it has infected 1,595 people in more than 20 countries and caused 571 deaths. Although the majority of human cases of MERS have been attributed to human-to-human infections, camels are likely to be a major reservoir host for the virus and an animal source of MERS infection in humans.

A team of scientists from the University of Liverpool and institutions in the USA, Kenya and Europe, surveyed 335 dromedary - single humped - camels from nine herds in Laikipia County, Kenya and found that 47% tested positive for MERS antibodies, showing they had been exposed to the virus.

Professor Eric Fèvre, Chair of Veterinary Infectious Diseases at the University's Institute of Infection and Global Health said: "Although Laikipia County camel density is low relative to more northern regions of Kenya, our study suggests the population is sufficient to maintain high rates of viral transmission and that camels may be constantly re-infected and serve as long term carriers of the virus. MERS in camels, it seems, is much like being infected by the common cold.

"The significance of this is not yet clear, because we don't know if the virus is universally zoonotic. While the risk of these camels spreading MERS to humans cannot yet be discounted, it appears to be, for now, very low as there have been no human cases diagnosed in Kenya. "It might be that the mutations required to make this virus zoonotic have only evolved recently in the Middle East, where the human outbreaks have so far been concentrated."

Lead author Dr Sharon Deem, Director of the Saint Louis Zoo Institute for Conservation Medicine, said: "Demand for livestock products, such as meat and milk, is rising across the globe and could offer poor farmers a route out of poverty as markets expand, but zoonotic disease remains a major obstacle to this goal.

"Further research to determine whether the MERS virus is dangerous to humans in Kenya and other sub-Saharan countries is critical."

The full study is published in PLOS ONE.

http://bit.ly/1KfOXWS

When You Space Out, Parts of Your Brain go to Sleep

Midday drowsiness might mean you're already drifting off

By Danny Lewis

If you have ever found yourself spacing out when you are tired, it's because parts of your brain are going to sleep. A newly-discovered brain circuit triggers pockets of the brain to go to sleep while the rest of it keeps powering through the day, according to a study published this week in the journal eLife. These results could help scientists develop better sleep aids. For many people, sleep feels like an all-or-nothing situation: Either you are awake or you are asleep. But as it turns out, your brain doesn't just switch off when you go to bed.

When you are asleep, in a coma, or under anaesthesia, a part of the brain called the thalamic reticular nucleus (TRN) starts sending slow brain waves to the brain's cortex. These "slow waves" are the same signals that trigger deep sleep and may help the brain solidify memories. When slow waves are activated while you're awake, they still send parts of your brain to sleep, making you feel drowsy, Andrew LeSane writes for Mental Floss.

"When you induce these slow waves across the cortex, animals start to behaviorally act like they're drowsy. They'll stop moving around, their muscle tone will go down," study author Laura D. Lewis says in a statement. "I'm inclined to think that happens because the brain begins to transition into sleep, and some local brain regions become drowsy even if you force yourself to stay awake."

To test whether the TRN could cause daytime drowsiness, Lewis and her group tried stimulating the region in mice to see whether the rodents would get sleepy. When they triggered the TRN, the mice's brains produced slow waves, making the mice spacy and drowsy. Not only does this seem to be the reason you might reach for that 3 P.M. coffee, but it suggests that the TRN can send people into a deep, dreamless sleep much like anaesthesia, Samantha Olson writes for Medical Daily.

"The TRN is almost certainly a site of action of many anesthetic drugs, given that a large classes of them act at these synapses and produce slow waves as one of their characteristic features," study co-author Emery Brown says in a statement.

While anaesthetics are a critical part to many modern medical treatments, scientists still don't completely understand why they work. But if scientists are able to use the TRN to send people to sleep like their mice, it could help make anaesthetics and sleep drugs that better mimic natural sleep patterns and have fewer side effects.

http://bit.ly/1W0lZ9C

People with Parkinson's walk again after promising drug trial

An expensive cancer drug may reverse late-stage Parkinson's disease, enabling participants in a small clinical to speak and walk again for the first time in years.

While there are several treatments for the symptoms of Parkinson's, if confirmed this would be the first time a drug has worked on the causes of the disease.

"We've seen patients at end stages of the disease coming back to life," says Charbel Moussa of Georgetown University Medical Center in Washington DC, who led the trial.

The drug, called nilotinib, works by boosting the brain's own "garbage disposal system" to clear proteins that accumulate in the brains of people with Parkinson's disease, says Moussa. These proteins are thought to trigger the death of brain cells that make molecules like dopamine that are needed for movement and other functions.

Nilotinib is already approved to treat cancer – it blocks a protein that drives chronic myeloid leukaemia. It also blocks another protein that interferes with lysosomes – cell structures that destroy harmful proteins. Moussa thinks that nilotinib can free up lysosomes to do a better job of clearing out proteins associated with Parkinson's disease.

Fast improvement

Tests in animals showed promise, so Moussa, his colleague Fernando Pagan and their team set up a small trial of 12 volunteers with Parkinson's disease or a similar condition called dementia with Lewy bodies. The trial was designed to test only the safety of the oral drug, which was given as a daily dose for six months.

Although all the volunteers were at an advanced stage of disease at the start of the trial, and three of them were unable to speak, all of them started to improve once they started taking the drug, some as little as three weeks later.

"We had people as stiff as a board at the start of the study who were walking around, sitting down and bending their legs by the end," says Moussa, "You could see the elation on their faces when they saw the improvement. There wasn't a dry eye in the room."

"They were brighter and more fluent in speech, and they had a lot more energy," says Pagan. All three of the participants who were unable to speak had begun talking again by the end of the trial. "It was like an awakening for them," says Pagan.

New lease of life

Alan Hoffman, who first showed signs of Parkinson's in 1997, says the nilotinib trial changed his life. As his disease worsened, he had many falls, needed his wife's help to get out of bed and he considered taking his own life. While deep brain stimulation helped treat the rigidity of his body, it wasn't a cure, so he enrolled in the nilotinib trial. Within a matter of weeks, he was able to make the bed, and read a book for the first time in years.

The drug was detectable in the cerebrospinal fluid of the participants, showing that it was making it through the blood-brain barrier and into the brain. The team also monitored the tau, amyloid beta, and alpha-synuclein proteins that accumulate as part of Parkinson's disease, and found that the levels of these proteins either stabilised or fell in all participants. At the same time, dopamine levels increased. Those taking the highest dose of the drug showed the biggest changes.

Pagan presented the results at the Neuroscience 2015 meeting in Chicago on Saturday. By one measure, participants' cognition improved by an average of around five points, on a scale of 30. While nilotinib causes unpleasant side effects in people who take high doses of it for leukaemia, much lower doses were used in this trial and the team saw no unwanted effects.

Graham Kerr at Queensland University of Technology in Brisbane, Australia, says the results are striking. "The new treatment certainly appears to alleviate symptoms of Parkinson's as well as cause reduction in biomarkers associated with disease progression," he says.

Too good to be true?

The team thinks it is the first drug that can target the root cause of Parkinson's disease and provide more than temporary relief. Other neurologists are excited by the results, but warn that no firm conclusions can be drawn until the drug has been tested in a larger trial with a placebo control.

"It seems too good to be true. I dearly hope I am wrong," says Carl Clarke of Sandwell and West Birmingham Hospitals NHS Trust, UK. "If it can really reverse Parkinson's, we'd have reached a major milestone, but I'm sceptical," says Kallol Ray Chaudhuri at King's College London. "I would say 'watch this space'."

There have been false dawns for Parkinson's before. A compound thought to encourage the growth of new brain cells – GDNF – received a lot of interest after promising animal experiments, and evidence suggesting it worked in a small number of people. However, no one has managed yet to replicate the effects in larger, placebo-controlled clinical trials.

The placebo effect can make a huge difference to symptoms of Parkinson's disease, says Arthur Roach, director of research at British charity Parkinson's UK. "We can't yet say that patients will benefit."

Moussa's team is now enrolling people with a range of disorders that involve accumulating brain proteins, including Alzheimer's disease and amyotrophic lateral sclerosis, for a larger, placebo-controlled trial.

Expensive treatment

Sadly, the effect doesn't last, and when the volunteers were taken off the drug at the end of the trial, they started to deteriorate again, says Moussa. Many have since tried to get hold of the drug themselves, but it costs a whopping $10,000 a month.

"One woman sold her car to buy the drug for her husband," says Moussa. Pagan is in discussions with manufacturer Novartis, hoping that the participants can be offered continued treatment at a reduced cost on a compassionate basis, through a procedure the company already uses to help people with cancer afford their medication. "We've been working on it for three months," says Pagan, "and hope to have an answer soon."

http://www.eurekalert.org/pub_releases/2015-10/aoa-rci100715.php

Researchers close in on a blood test for Alzheimer's disease

Early detection presents new opportunities to slow or perhaps even halt disease progression

Researchers from the Rowan University School of Osteopathic Medicine are nearing development of a blood test that can accurately detect the presence of Alzheimer's disease, which would give physicians an opportunity to intervene at the earliest, most treatable stage.

Robert Nagele, PhD, presented his team's most recent findings October 18 at OMED 15 in Orlando. Dr. Nagele's work focuses on utilizing autoantibodies as blood-based biomarkers to accurately detect the presence of myriad diseases and pinpoint the stage to which a disease has progressed. By detecting Alzheimer's disease long before symptoms emerge, Dr. Nagele hopes those with disease-related autoantibody biomarkers will be encouraged to make beneficial lifestyle changes that may help to slow development of the disease.

"There are significant benefits to early disease detection because we now know that many of the same conditions that lead to vascular disease are also significant risk factors for Alzheimer's. People found to have preclinical disease can take steps to improve their vascular health, including watching their diet, exercising and managing any weight and blood pressure issues to help stave off or slow disease progression," Nagele said.

While the cause of Alzheimer's remains elusive, it is clear that maintaining a healthy blood-brain barrier is a critical preventative measure. Diabetes, high cholesterol, high blood pressure, stroke and being overweight jeopardize vascular health. As blood vessels in the brain weaken or become brittle with age, they begin to leak, which allows plasma components including brain-reactive autoantibodies into the brain. There, the autoantibodies can bind to neurons and accelerate the accumulation of beta amyloid deposits, a hallmark of Alzheimer's pathology.

The blood test developed by Dr. Nagele has also shown promise in detecting other diseases, including Parkinsons's, multiple sclerosis and breast cancer. His team's research on the role of autoantibodies explains that:

All humans possess thousands of autoantibodies in their blood;

These autoantibodies specifically bind to blood-borne cellular debris generated by organs and tissues all over the body;

An individual's autoantibody profile is strongly influenced by age, gender and the presence of specific diseases or injuries; and

Diseases cause characteristic changes in autoantibody profiles that, when detected, can serve as biomarkers that reveal the presence of the disease.

In Alzheimer's, the brain begins to change years before symptoms emerge. Detecting Alzheimer's antibodies at the preclinical stage would give patients an opportunity to work with their physician to make lifestyle changes or receive available treatments before they become symptomatic. Potentially, this early intervention could help those with preclinical Alzheimer's avoid or delay the most devastating symptoms.

"As osteopathic physicians, we constantly tell patients that a healthy lifestyle is the best medicine for preventing disease. We also know that many people tune out messages about nutrition and exercise until a health crisis gets their attention," said Jennifer Caudle, DO, assistant professor of family medicine at Rowan University. "I can't think of a single patient who wouldn't take steps to prevent the progression of Alzheimer's if they could directly affect their prognosis."

Today, there is no definitive FDA-approved blood test for Alzheimer's, which affects an estimated 5.3 million Americans. It is among the top 10 causes of death in America.

Dr. Nagele's research has been supported by grants from the Michael J. Fox Foundation and the Osteopathic Heritage Foundation.

http://www.eurekalert.org/pub_releases/2015-10/uotm-flc101615.php

For lung cancer patients, IMRT associated with lesser side effects, better tolerance of chemotherapy, compared to conventional radiation therapy

Findings encourage practice change for lung cancer management

An analysis of an international, cooperative-led trial of patients with locally advanced non-small cell lung cancer (NSCLC) has shown that those who received intensity modulated radiation therapy (IMRT) had less severe lung toxicity and were able to better tolerate their chemotherapy, compared to patients who received 3-dimensional conformal radiation therapy (3-D CRT).

Stephen Chun, M.D., fellow, Radiation Oncology at The University of Texas MD Anderson Cancer Center, presented the research at the American Society for Radiation Oncology's 57th Annual Meeting.

According to the American Cancer Society, in the United States, 221,200 will be diagnosed with lung cancer in 2015 and 158,040 will die from the disease - making it the deadliest of all cancers. About a third of all lung cancers are diagnosed when the cancer is locally advanced, said Chun. The standard of care for locally advanced lung cancer is concurrent chemotherapy and radiation, with most patients receiving either 3-D CRT or IMRT.

For decades, 3-D CRT has been the standard of care for the treatment of lung cancer. The technique shapes radiation beams aimed in straight lines to match the shape of the tumor. In contrast, IMRT is a newer, more-advanced technique that sculpts and molds radiation beams to tumor targets, using substantially more complex radiation beam arrangements than 3D-CRT. In turn, IMRT can spare more normal tissue than 3D-CRT with high doses of radiation, explained Chun.

"IMRT was developed more than a decade ago and because it's been shown to reduce toxicity, it has been accepted to treat prostate, brain, and head & neck cancers," said Chun, the study's lead author. "There have been a number of smaller studies, including research led by MD Anderson, looking at IMRT and lung cancer. This the first analysis of a prospective clinical trial to show a reduction of toxicity associated with IMRT in locally advanced lung cancer and could lead to a major change in the way radiation therapy is delivered for the disease.

"The data from our study makes a strong argument that we should routinely consider use of IMRT in locally advanced lung cancer," Chun continued.

This study is a secondary analysis of data collected from the NRG/RTOG 0617, a large, multi-center phase III randomized trial of patients with locally advanced NSCLC. The study originally enrolled patients from 2007 to 2011 and compared a high dose of 74 Gy to the standard dose of 60 Gy. All underwent concurrent chemotherapy (carboplatin/paclitaxel, with or without cetuximab) and either 3-D CRT or IMRT. In the study, NRG/RTOG 0617, 482 patients were treated with radiation - 53 percent with IMRT and 47 percent with 3-D CRT.

The study found 44 percent fewer cases of severe pneumonitis (defined by the researchers as lung inflammation that required oxygen, steroids or mechanical ventilation, and/or led to death) in patients who received IMRT - 3.5 percent of patients, despite having larger tumors, compared to 7.9 percent of the 3-D CRT group. While the benefit of IMRT was seen in all tumor sizes, the reduction of severe pneumonitis was more pronounced in larger tumors, explained Chun.

Additionally, those who received IMRT were more likely to complete consolidative chemotherapy - 37 percent, compared to 29 percent in those treated with 3D-CRT. High dose chemotherapy after completing chemotherapy with radiation, is considered to be standard for locally advanced lung cancer.

One of the principles of IMRT, explained Chun, is to bring in many complex beams to converge on a target, producing a high dose on the target and dramatically sparing nearby adjacent tissue. By using multiple beam arrangements, this leads to spreading of a low-dose bath such as the volume of lung that received 5 Gy of radiation.

"It's been unclear what the consequences of that low dose bath are. What we've seen in this study is that indicators of the low dose bath that's increased by IMRT had no association with any severe toxicity outcome. This finding suggests that we should be optimizing radiation treatment by the high and intermediate dose region, and not the low dose region," said Chun.

IMRT is more time-intensive and costly, said Chun, yet the study showed a dramatic reduction in severe toxicities. These findings have the potential to reduce the number of hospital admissions and improve quality of life for this patient population, he explained.

In addition to Chun, additional MD Anderson authors include Ritsuko U. Komaki, M.D., Radiation Oncology. Additional authors include: Hak Choy, M.D., and Puneeth Iyengar, M.D., Ph.D., University of Texas Southwestern Medical Center, Dallas; Chen Hu, Ph.D., and Rebecca Paulus, NRG Oncology, Philadelphia; Robert Timmerman, M.D., University of Texas Southwestern School of Medicine, Dallas; Steven E. Schild, M.D., Mayo Clinic, Phoenix; Jeffrey A. Bogart, M.D., SUNY Upstate Medical University, Syracuse; Michael C. Dobelbower, M.D., University of Alabama at Birmingham; Walter R. Bosch, D.Sc., and Clifford G. Robinson, M.D., Washington University School of Medicine, St. Louis; James M. Galvin, D.Sc., IROC Philadelphia RT; Vivek S. Kavadi, M.D., Texas Oncology, Fort Worth; Samir Narayan, M.D., Michigan Cancer Research Consortium, Ann Arbor; Raymond Wynn, M.D., University of Pittsburgh Medical Center; Adam Raben, M.D., Christiana Care Health System, Newark; Mark Augsperger, M.D., Baptist Cancer Center, Jacksonville; Robert M.

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Arm mole count 'predicts skin cancer risk'

Having more than 11 moles on one arm indicates a higher-than-average risk of skin cancer or melanoma, research suggests.

Counting moles on the right arm was found to be a good indicator of total moles on the body. More than 100 indicates five times the normal risk.

The study, published in the British Journal of Dermatology, used data from 3,000 twins in the UK. GPs could use the findings to identify those most at risk, it said.

Melanoma is a type of skin cancer affecting more than 13,000 people in the UK each year.

It develops from abnormal moles, so the risk of being diagnosed with a melanoma is linked to the number of moles a patient has.

Researchers from King's College London studied a large group of female twins over a period of eight years, collecting information on skin type, freckles and moles on their bodies.

After repeating the exercise on a smaller group of around 400 men and women with melanoma, they came up with a quick and easy way to assess the risk of skin cancer.

Moles, freckles and melanoma

Freckles are small usually pale brown areas of skin, which are often temporary and are usually linked to sun exposure

Moles are small coloured spots on the skin made up of cells called melanocytes, which produce the colour (pigment) in your skin. They are long-lasting and are not directly linked to sun exposure

Moles can be flat, raised, smooth or rough and may have hair growing from them

They are usually brownish in colour and are circular or oval with a smooth edge

Most moles are completely harmless

If you notice any changes to your moles or a worried about them, see your GP

Things to look for: Uneven colouring, uneven or ragged edges, bleeding, itching, enlargement

Source: NHS Choices

Females with more than seven moles on their right arm had nine times the risk of having more than 50 on their whole body. Those with more than 11 on their right arm were more likely to have more than 100 on their body in total, meaning they were at a higher risk of developing a melanoma.

The findings could help GPs to identify those with an increased risk of developing a melanoma.

Sun safety

What sun protection factor should I use?

The higher the sun protection factor (SPF), the more protection you get. Use sunscreen with a SPF of at least 15. Use broad-spectrum sunscreens, which protect against harmful UVA and UVB rays.

How long can I stay in the sun?

No longer than you would without sunscreen. Sunscreen should not be used as an excuse to stay out in the sun - it offers protection when exposure is unavoidable. The summer sun is most damaging to your skin in the middle of the day.

What should I do if I get sunburn?

Paracetamol or ibuprofen will ease the pain by helping to reduce inflammation caused by sunburn. Sponge sore skin with cool water, then apply after sun or calamine lotion. If you feel unwell or the skin swells badly or blisters, seek medical help. Stay out of the sun until all signs of redness have gone.

Should I cover up my mole when I'm in the sun?

If you have lots of moles or freckles, you're more likely to develop skin cancer, so you need to take extra care. Avoid getting caught out by sunburn. Use shade, clothing and sunscreen with an SPF of at least 15. Keep an eye out for changes to your skin and report these to your doctor without delay.

Source: NHS

Lead author Simone Ribero, of the department of twin research and genetic epidemiology at King's, said: "The findings could have a significant impact for primary care, allowing GPs to more accurately estimate the total number of moles in a patient extremely quickly via an easily accessible body part."

Consultant dermatologist and study co-author Veronique Bataille said if a patient was worried about an abnormal mole and went to see their GP, counting moles on one arm "might ring alarm bells" and highlight those patients who should be seen by a specialist more quickly.

Dr Claire Knight, health information manager at Cancer Research UK, said the study findings were helpful, but added that fewer than half of melanomas develop from existing moles.

"It's important to know what's normal for your skin and to tell your doctor about any change in the size, shape, colour or feel of a mole or a normal patch of skin," she said.

"And don't just look at your arms - melanoma can develop anywhere on the body, and is most common on the trunk in men and the legs in women."