PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.

Cambridge Branch Newsletter – September-October 2021

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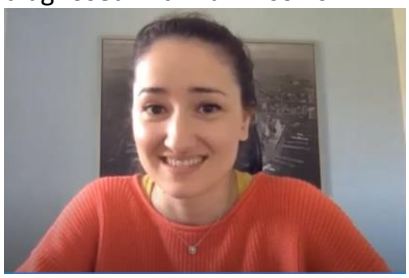
BRANCH MEETINGS

WERE YOU TOLD ABOUT EXERCISE?

We all know exercise is a Good Thing. Lots of us know we should do more of it. But how many of us were told when first diagnosed that it is potentially of real significance to People with Parkinson's (PwP)? That it might just be that exercise is the best method we have to slow down progression?

This is the background to work being done by Ledia Alushi (pictured), a physiotherapist now studying for a PhD at Cambridge University, titled 'The role of physical health education for people newly diagnosed with Parkinson's'.



"In the last 10 years there have been many studies showing that exercise can improve both motor symptoms like gait and balance, and non-motor ones like apathy and depression, and cognitive functions," Ledia told the Branch Meeting on July 22.

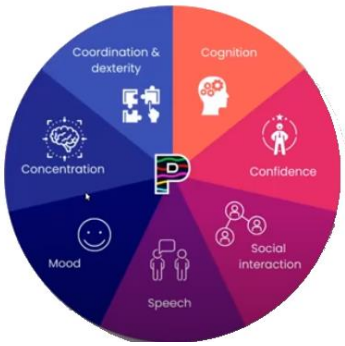
More specifically, mice models have shown that exercise can partially prevent the development of L-dopa-induced dyskinesia. Also, clinical studies have suggested exercise may increase the efficiency of L-dopa, and enhance brain neuroplasticity and the level of neurotrophic factors like BDNF. Despite this, a recent study showed that nearly 50% of people said they had not received any education about exercise, or were not sure they had.

So Ledia is launching her own survey aiming to clarify people's needs and preferences about exercise, note any education they received at diagnosis, and ultimately co-design with PwP and others a programme to promote exercise. To participate, contact her at la463@cam.ac.uk, tel: 07931-709730. It will involve an online questionnaire, taking about 20 minutes to complete, and possibly an online interview, or taking part in a focus group.

THE SEVEN WONDERS OF PARKINSON'S ART

At the July 9 meeting, we were told about the creation and development of Parkinson's Art, which is now run by Trevor Willard. He was diagnosed about 10 years ago at the age of 38. His working background is in computers, with no involvement in the art world. But three years ago he took up painting, and he now runs the Parkinson's Art Group, as well as working for Parkinson's UK. The aim is to promote the arts of all kinds by providing a free platform enabling people to express themselves. It is run by writers and artists, all PwP.

Getting involved in the arts has a whole series of benefits, Trevor said, as depicted in the seven wonders of art diagram (below).



The website that serves as the platform is www.parkinsons.art. It is free to anyone who wants to put their work on show. It features a shop for selling items produced by Parkinson's Art members, an online magazine called Hue's Talking, and details about events and competitions that are run throughout the year. One that has just finished was called Vivid Dreams, which ran for two weeks at the Oxo Tower in London.

100 PLUS YEARS OF LOCAL HISTORY

For those interested in the history of our region, the first August meeting was one not to miss. It featured Mike Petty, and few people can match his knowledge of Cambridgeshire, which he has been studying and collecting information on for around 70 years. It was in 1964 that he discovered a huge collection of papers going back 110 years, which was

invaluable – but had never been sorted. He took on the task, and spent the next 30 years at it!

Today we have access to a research tool – the Internet – that people could only dream about in the past. But anyone looking to do their own research could start by dipping into these: Mike's own books, such as his Millennium History of Stretham (his local village); Annals of Cambridge by Charles Henry Cooper (several volumes); the Cambridgeshire Collection, available at the public library; the Cambridge Independent newspaper; Mirror Pix of Watford; the Chronicles series of booklets; Facebook for Fenland History and Cambridge: a Chronicle; and the Cambridge University Library, which includes the digital resource called 'Raven'. hhowever hard you work at it, it will take you a long time to match Mike's own digitised collection – which he reckons now stands at around 2000 books. And he is rarely parted from it – he carries it with him, stored on a USB memory stick on his keyring!

NEWS, EVENTS & PEOPLE

WANDLEBURY WALK ON SEPTEMBER 25

A series of fund-raising Walks for Parkinson's are

taking place across the country including a local one at Wandlebury Country Park on Saturday, September 25, at 11am. To enter, you must register before September 19 – £12 for adults, £6 for under 18s, and the minimum sponsorship target is £50. Every pound raised will be matched by the Frank & Evelyn Brake Connect Fund. You can walk one of two routes, 1.5 or 4.5 miles, and COVID-19 guidelines will be followed. Details will be confirmed to participants a week before the event. Any questions, call 0800-138-6593 or email fundraising@parkinsons.org.uk.

JustGiving PAGE NOW RAISING FUNDS

Another fund raising source is the JustGiving page we have recently set up (https://www.justgiving.com/fundraising/parkinsonscambridge). This makes it easy to donate in a simple, fast and totally secure way, and enables us to claim Gift Aid on your donation. Your details are totally safe with JustGiving – they will never sell them on or send unwanted emails. Once you donate, your money is sent to Parkinson's UK who will then forward it onto the Branch. The site has already raised thousands.

SUPPLEMENT FEATURES DIGITAL TECHNOLOGY

A special supplement to the Journal of Parkinson's Disease (JPD) reviews how digital technology is being used to reshape research and clinical care. 'Digital health technology' is an umbrella term that spans many applications, including wearable sensors, non-contactable domestic sensors, smartphone apps, video-conferencing and other telemedicine systems that make possible remote interaction between patients and healthcare providers.

"Despite accumulating evidence to support the feasibility and benefits of digital technology

approaches, its use in clinical practice has remained scarce," said joint JPD Editor-in-Chief, Bastiaan Bloem. "It has taken a contagion to make patients, physicians, and insurers pay better attention. The limits on our ability to travel imposed by the ongoing coronavirus pandemic has dramatically increased the use of digital platforms in a few months. This change was unprecedented and has been one of the few silver linings of the pandemic."

A specific example is the use of wearable sensors, enabling clinicians to monitor patients' motor symptoms while they are at home, and gain insights into behavioural changes and the implications of social distancing on patients' non-motor symptoms. For example, assessing sleep can now be done in the home, passively, and frequently, expanding the knowledge of sleep disorders in PwP.

New tools may also reveal more about features of Parkinson's that have largely been invisible, such as the appraisal of social function, expanded assessments of voice, tremor, falls, dyskinesia or freezing of gait, and objective measurement of the response to treatment. This could improve understanding of the condition, its temporal pattern, variability, and impact on individuals.

“We can say with certainty that the digital revolution has definitely started,” Bloem said. “We can almost be equally certain that this is only the beginning. Digital medicine will benefit patients and healthcare in ways that are currently difficult to predict.”

SCIENCE & RESEARCH

NEW TECHNIQUES ARE NON-INVASIVE

Two new non-invasive techniques for brain stimulation are being developed in the US, both potentially valuable for treating Parkinson's. The first uses focused, low intensity ultrasound (FUS) to raise the temperature of specific types of neurons, and thereby activate them. This enables the researchers to precisely control the motor activity of mice, without surgical implantation.

Researchers at Washington University in St Louis claim to be the first to have activated specific cells in the brains of mammals by this combination of ultrasound-induced heating effect and genetics. They call the technique sonothermogenetics, and have shown that it can control behaviour by stimulating specific targets deep in the brain.

“Sonothermogenetics has the potential to transform our approaches for neuroscience research and uncover new methods to understand and treat human brain disorders,” they say.

Using a mouse model, the team delivered low-intensity FUS signals to genetically selected neurons via a wearable device, which acted as a switch to turn the neurons on or off. The FUS device is worn on the head of free-moving mice and it can target different locations in the whole brain, affecting their behaviour. Because it is non-invasive, this technique has the potential to be scaled up to humans in the future.

It builds on work several years ago, which demonstrated that FUS alone could lead to new, non-invasive ways to control the activity of specific cells. FUS modulated the currents flowing through the brain cell channels by up to 23%.

The work also builds on the recently developed technique of optogenetics, which also makes it possible to stimulate neurons in the brain. Optogenetics has led to the discovery of new neural circuits, but its penetration is limited because of light scattering, and requires surgical implantation of optical fibres. Sonothermogenetics has the potential to target anywhere in the brain with millimeter-scale precision and without causing any damage.

Meanwhile researchers at the Indiana University School of Medicine are developing a non-invasive stimulation technique with the ultimate aim of treating Parkinson's and other brain conditions such as epilepsy and Alzheimer's disease.

This technique uses a new type of magnetoelectric nanoparticles that can be delivered to a specific part of the brain using a magnetic field. Then a magnetic wave is emitted to stimulate neural activity in that particular area of the brain.

When a brain injury or neurodegeneration occurs, the damage to the brain can result in hyper (excessive) excitability, which underlies neurological disorders such as neuropathic pain and epilepsy.

“The conventional treatment is mainly to try to directly inhibit such hyperexcitability,” a researcher said. “But we found the initial damage was caused by a loss of brain tissue, and this causes the nervous system to compensate for loss of function by working harder. So we actually need to stimulate activity, not inhibit it.”

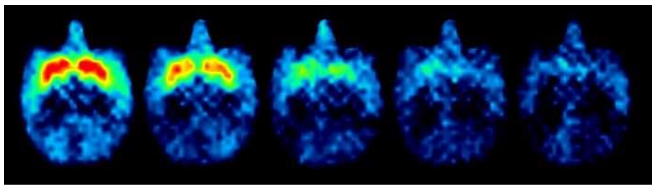
The method is non-invasive, good for stimulating deep brain function, and more efficient than traditional methods of brain stimulation, with no need for genetic manipulation. The nanoparticles used are the only ones that make it possible to stimulate the brain without any invasive procedures. Once injected as a solution into a vein, you can then direct them to any part of the body. So if you put a magnet on the head, you can deliver the nanoparticles to the required brain region. The team hopes to begin studying the method in humans in the next couple of years.

TO DO OR NOT TO DO: WHAT CONTROLS MOTIVATION AND DECISION-MAKING?

Why do we do things? What persuades us to make an effort to achieve goals? For example, what drives us to search for food? Neurologically, the answer is hidden in the reward system of the brain – an evolutionary mechanism that controls our willingness to work, or take a risk, which is the cost of achieving a goal, and enjoying the perceived reward. In people suffering from depression, schizophrenia, or Parkinson's, this reward system is often impaired, reducing motivation for work, or chronic fatigue.

To overcome these debilitating effects, neuro-scientists are investigating the reward system, to work out how it evaluates the cost-benefit trade-off involved when we decide whether to pursue a task.

One group based at the Japanese National Institutes for Quantum and Radiological Science and Technology is focusing on dopamine, seen as the substance that plays the key role in inducing motivation and regulation of behaviour based on cost-benefit analysis (see the article on page 6).



PET scans show the blocking of dopamine receptors, which affects the decision-making process.

Using macaque monkeys as models, the researchers targeted the roles of two classes of dopamine receptors believed to be involved in cost-benefit motivation, called D1 and D2. They trained the animals to perform tasks so they could measure how the perceived size of the reward, and the effort needed to get it, influenced their behaviour.

Then they systematically manipulated the monkeys' D1 and D2 receptors by injecting them with molecules to dampen their responses to dopamine. Using PET imaging, they measured how much the receptors were affected. They gave the monkeys the chance to perform tasks for rewards and noted whether they accepted or refused to perform them, and how quickly they responded to the cues related to the tasks.

The experiments revealed that this kind of cost-benefit decision-making involved both D1 and D2 receptors, in terms of motivation to perform the tasks, and in increasing 'delay discounting'. This is the tendency to prefer immediate, smaller rewards over larger but delayed rewards. They also showed that dopamine-based signalling between D1 and D2 regulates the assessment of benefits – 'reward availability' – and costs, or 'energy expenditure'. But 'discounting' – the lessening of a reward's value because of the effort needed to get it – was only related to D2.

This work may seem somewhat esoteric, but the researchers say it will potentially help to decipher the pathophysiology of psychiatric disorders. This could make it possible to manipulate the brain's reward system, and so enhance motivation levels, improving the quality of life for many people.

AbilityNet HELPS WITH TECHNOLOGY

The AbilityNet organisation operates a UK-wide network of more than 300 DBS-checked (Disclosure & Barring Service) volunteers who provide free, one-to-one advice and support about technology that can help people with varying conditions. In particular, they will help connect people with the Internet, in their own homes, giving them online contact with other people and all the essential services and information available. They can also give specialist advice on adapting technology for those living with long-term impairments to their vision, hearing, cognitive or movement capacities.

AbilityNet helps disabled and older people get the most from their computer, smartphone or tablet.

All this is done in a highly personalised way, at each individual's pace. Contact details are: (freephone) 0800-048-7642, enquiries-@ability.org.uk, https://ability.org.uk, Facebook and twitter @abilitynet.

GEL FOR STEM CELL TREATMENT AND DBS

Gel is the order of the day. Researchers at the Australian National University (ANU) have developed a new form of hydrogel that they say could transform stem cell therapy for Parkinson's. The gel also has the potential to help stroke victims and other neurological conditions.

(continued page 5, 2nd column)

VIEWPOINT

In recent years, virtually everyone has had to use technology to interact with the outside world. (Apologies to any hermits reading this). So we all know it is becoming increasingly difficult to do anything without using technology.

For instance, try booking a holiday without the Internet, email, mobile phone, tablet or computer. It may still be possible. But I suspect that even if you didn't use technology yourself, you would probably find yourself paying someone else to do it for you.

COVID has made things even worse, requiring special forms to be filled in – online of course. And even if you are going to a country that doesn't require you to have a test (or tests) just before you go, you still have to order and pay for at least two, to enable you to return to Britain. Then you have to book your plane seats, provide passport details and other identity information, etc, etc.

So what about people who still don't use electronic communication devices and the Internet? It is not at all cynical to say: they are simply being forgotten. The commercial world seems to take the view that they can comfortably be ignored. You can virtually hear the marketing executives thinking: "They're a small, unimportant part of our market. And they're old, so they won't be with us much longer."

On their behalf, I feel distinctly annoyed, even furious. How did it come to this – that you can only deal with the world if you purchase a product that you don't want, indeed one that you actively dislike? One that in some respects has had some awful effects: from the trivial – the infernal nuisance of mobile phones on trains, in restaurants etc – to fostering the positively poisonous. I am referring of course to the anger that so many people give vent to on social media, protected as they are by anonymity. Not to mention others like Fake News. And I speak as someone who has been a technology journalist for the last 40 years!

It has even reached the point where companies blithely assume you must have a smartphone, not just a mere computer. Sky TV, for example, gives loyalty 'prizes' to people who have remained customers for a number of years. But they only reveal what these prizes are in a smartphone app. If you 'only' have a desktop computer and a simple mobile phone for making calls, you cannot find out what they are. (The fact that most of them are not worth having is beside the point).

Some branch members do not have the facility to receive the newsletter electronically. So we print out scores of copies and 'snail mail' them. Long may they stay that way. Sometimes I am tempted to join them!

(from page 4)

The new material is made from natural amino acids, the building blocks of proteins. It acts as a gateway to allow the safe transfer of stem cells into the brain and the restoration of damaged tissue by releasing the growth-enabling protein, GDNF. By putting the stem cells into a gel, they are exposed to less stress when injected into the brain and are more successfully integrated.

When the hydrogel is shaken, it turns into a liquid which allows it to be injected into the brain through a very small capillary using a needle. Once inside the brain, the gel returns to its solid form and provides support for the stem cells that replace lost dopaminergic neurons. This has increased survival rates for these neurons. The hydrogel also has the potential to treat stroke patients and damaged knees or shoulders, following successful animal trials.

"When we introduced the gel technology with the stem cells we saw a huge improvement in the animals' coordinated paw movement and overall motor function recovery," said Professor David Nisbet, pictured. The hydrogel technology is cost-effective and easy to manufacture on a mass scale, and it is hoped it will soon be available in hospitals, after clinical trials.

Meanwhile another hydrogel device is claimed to be a better option for Deep Brain Stimulation (DBS) than the electrodes currently used, as it triggers less of a reaction and reduces scarring. When electrodes are inserted in the DBS process, the brain reacts by surrounding them with scar tissue, slowly degrading their ability to record and stimulate brain patterns.

The new device consists of an optical fibre that uses light to control specific nerve cells, electrodes to record brain signals, and a tiny microfluidic channel to deliver drugs directly to the brain.

The hydrogel is solid while dry, enabling the scientists to surgically implant it into the brains of

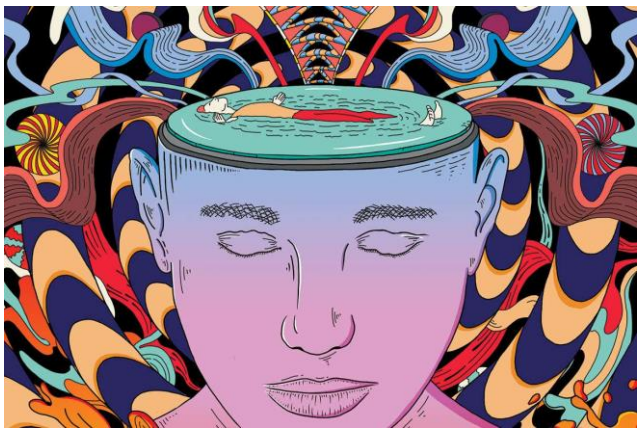
mice. Once implanted, it absorbs body fluids, which make it mimic the surrounding tissue. This absorption, along with the hydrogel's flexibility, results in less scar tissue and enables the fibre bundle to remain close to its target site, allowing it to track brain signals over longer periods of time.

This was first time a hydrogel has been used as part of a multifunctional neural interface probe, and it increased its lifespan dramatically. The device also has potential for drug delivery, with a chemical cocktail that reduces anxiety behaviour in mice being implanted into their brains.

TAKE A TRIP WITHOUT GOING ANYWHERE

A new drug is being developed by a US company, Akome Biotech, as a potential treatment for Parkinson's. So what's new? Scores of new drug formulations are produced every year. But this one is a bit different – if you were to take it, you would be likely to go on a trip, without leaving your armchair. That is because the drug is a psychedelic.

Psychedelics, also known as hallucinogens, are substances that produce changes in perception, mood and cognitive and emotional states. Akome's new drug contains 'N, N-dimethyltryptamine', known as DMT, a psychedelic that induces a rapid and intense trip characterised by visual hallucinations.



DMT's effects have earned it the name 'spirit molecule'. It is found in many plants and animals, but can be produced synthetically. It is also known as ayahuasca, a South American psychoactive brew used for ceremonial spiritual medicine among the indigenous peoples of the Amazon basin.

According to the company, preliminary research suggests that its drug, which it calls AKO004, may play a neuroprotective role in the brain that could preserve nerve function in Parkinson's patients.

Currently, DMT has no approved medical use in the US, but in the UK, a clinical trial is investigating the compound's safety, tolerability, and efficacy for the treatment of depression. The drug is said to act as an antioxidant and decrease neurodegeneration. Antioxidants inhibit oxidation, a reaction that can damage cells. Initial analysis suggests that AKO004 may also preserve neuron structure and/or function.

Akome is a biotechnology research company that focuses on developing psychedelic medicines for treating mental health and neurological conditions, such as Parkinson's, Alzheimer's, stroke and depression.

DOPAMINE: THE EXTRAORDINARY SUBSTANCE WE HAVEN'T GOT ENOUGH OF

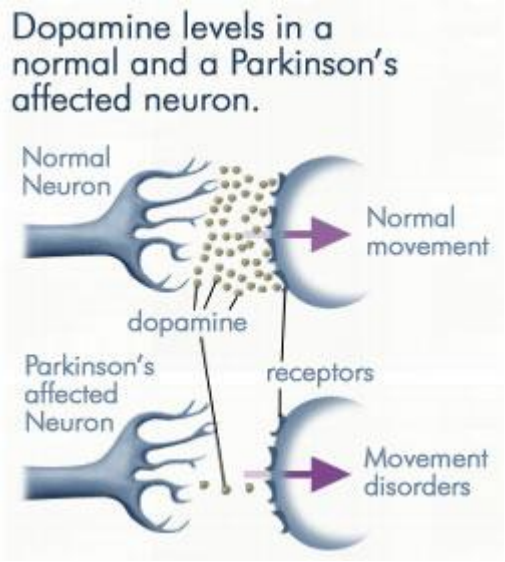
As we all know, Parkinson's occurs because of a lack of dopamine in the brain. What we don't know, in most cases, is what causes this to happen. That is why the majority of cases are called 'idiopathic', meaning of unknown origin. The root cause of Parkinson's may be a mystery, but the same thing can't be said about dopamine itself. Over the last several decades, science has revealed a considerable amount about this rather extraordinary substance, and what a critical role it plays in many physical situations and conditions.

The first thing to know about dopamine is that it is a neurotransmitter. That means it is a chemical released by neurons (brain cells) to send signals to other nerve cells. Neurotransmitters are synthesised in specific regions of the brain, but affect many areas. Indeed, a host of mental and physical activities can be affected by dopamine, from learning, motivation and mood, to kidney function, control of nausea and sleep.

As PwP know only too well, the last on this list is by no means the least serious! Not only is dopamine involved in the functions listed above, it is also linked with several serious illnesses other than Parkinson's, even though it is probably the most commonly known one. The neurotransmitter has also been linked with schizophrenia – this time, it is an **excess of dopamine** that is thought to be involved**.** That is why most anti-psychotic drugs are **dopamine antagonists,** which aim to reduce the effects the substance is having**.** In contrast, many of

us take **dopamine agonists,** to help make maximum use of the dwindling amounts we still have.

Other conditions associated with dopamine are: restless legs syndrome, which affects some PwP; attention deficit hyperactivity disorder (ADHD); Tourette's – a strange condition which causes people to have tics, and make involuntary and uncontrollable sounds and movements. These can be inappropriate, for example obscene words and swearing (known as echolalia). Two others are bipolarity (also known as manic depression), and multiple sclerosis.



Dopamine and related substances are not always culprits. For example, antagonist drugs are effective anti-nausea agents, and dopamine itself is useful in treating heart failure or shock, especially in newborn babies. For this purpose, it has to be injected because it cannot cross the blood-brain barrier.

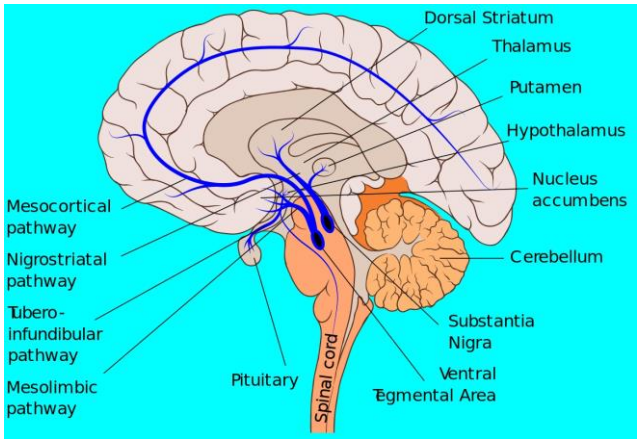
And relating to that inability is where one of the most significant developments in the treatment of Parkinson's occurs. That is because L-dopa, the drug that the vast majority of PwP take, **can cross the blood-brain barrier**. It makes it extremely unusual – most drugs cannot – but it is something all PwP should be deeply grateful for. If L-dopa couldn't, it would have been a major problem for what has been the single most effective treatment for Parkinson's, used since the late 1960s.

Dopamine is produced in several areas of the brain – there are even dopaminergic neurons in the retina – but the two largest, most important sources are the substantia nigra and the ventral tegmental area (pictured). One puzzle about dopamine is just how few cells there are that produce it, around 400,000. Given that the brain contains something like **100 billion cells,** it seems odd that there are so few of them – a tiny fraction of 1% – to produce such an important substance.

It could be that there is some evolutionary reason for this, as yet undiscovered. But dopamine is not a recent arrival on the evolutionary scene. It appeared as a neurotransmitter when the first nervous systems evolved around 500m years ago. It operates in living forms that range from corals and jellyfish to worms, molluscs and fruit flies. The last can be trained to repeat an action if it is consistently followed by an increase in dopamine levels.

A further profound feature associated with dopamine is precisely what it does. One popular theory is that it plays a key role in selecting action. It does this in two ways. First, it sets a 'threshold' for initiating action, so the higher the level of dopamine activity, the lower the impetus needed to generate a particular action. This means large amounts of dopamine lead to high levels of motor activity, and the result can be impulsive behaviour – which is why this is a potential side effect of dopamine agonists.

In contrast, low levels of dopamine lead to slowed reactions, causing the symptoms of Parkinson's, notably stiffness, difficulty initiating movement, and general bradykinesia. Freezing of gait (FoG) is a typical example. But interestingly, when PwP are confronted with a strong stimulus like a serious threat or other emergency, their reactions can be as quick and vigorous as those of a healthy person.



Another effect of dopamine is its role as a 'teaching signal'. Here, when a particular action is followed by increased dopamine activity, the brain circuits involved are altered so that a similar response

becomes easier to evoke when a comparable situation arises in the future.

Dopamine is closely connected with pleasure, with many kinds of pleasurable experiences increasing its release. Or should we put it the other way round: the release of dopamine results in the experience of pleasure? This is the age-old philosophical problem of the relationship between the mind and the body.

But leaving such philosophical conundrums aside, evidence for the pleasure connection is clear, examples including sex, eating, and playing video games! Also, antipsychotic drugs reduce dopamine levels and can cause a state called anhedonia – a diminished ability to experience pleasure.

However, there is nothing simple about the link between dopamine, pleasure and action. For example, if animals have one of their key dopamine-producing areas (the ventral tegmental) made inactive, they do not seek food and will starve to death if left alone. But if food is placed in their mouths, they will consume it and show expressions of pleasure!

Velvet beans, which contain L-dopa

Talking of food, lots of different plants and fruit contain dopamine. Bananas contain one of the highest levels at 40-50 parts per million (ppm) by weight. But before rushing out to buy pounds of them, remember that dopamine consumed via food cannot affect the brain, because it cannot pass through the blood brain barrier. However, there are plants containing L-dopa that can, such as the leaves and bean pods of velvet beans (pictured), and fava beans. Perhaps it's time we switched from the baked variety?

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Facebook: www.facebook.com/parkinsonsukcambridge/
Twitter: https://twitter.com/CambBranchPUK
Help Line 0808-800-0303 (free phone call) Specialist advisers can answer questions on any aspect of Parkinson's
Parkinson's Nurses in our area: for help and information contact the Parkinson's Nurse Team on 0330-726-0077
Addenbrooke's Hospital Parkinson's Nurses 01223-349814
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