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Repairing and treating damaged or dysfunctional brains
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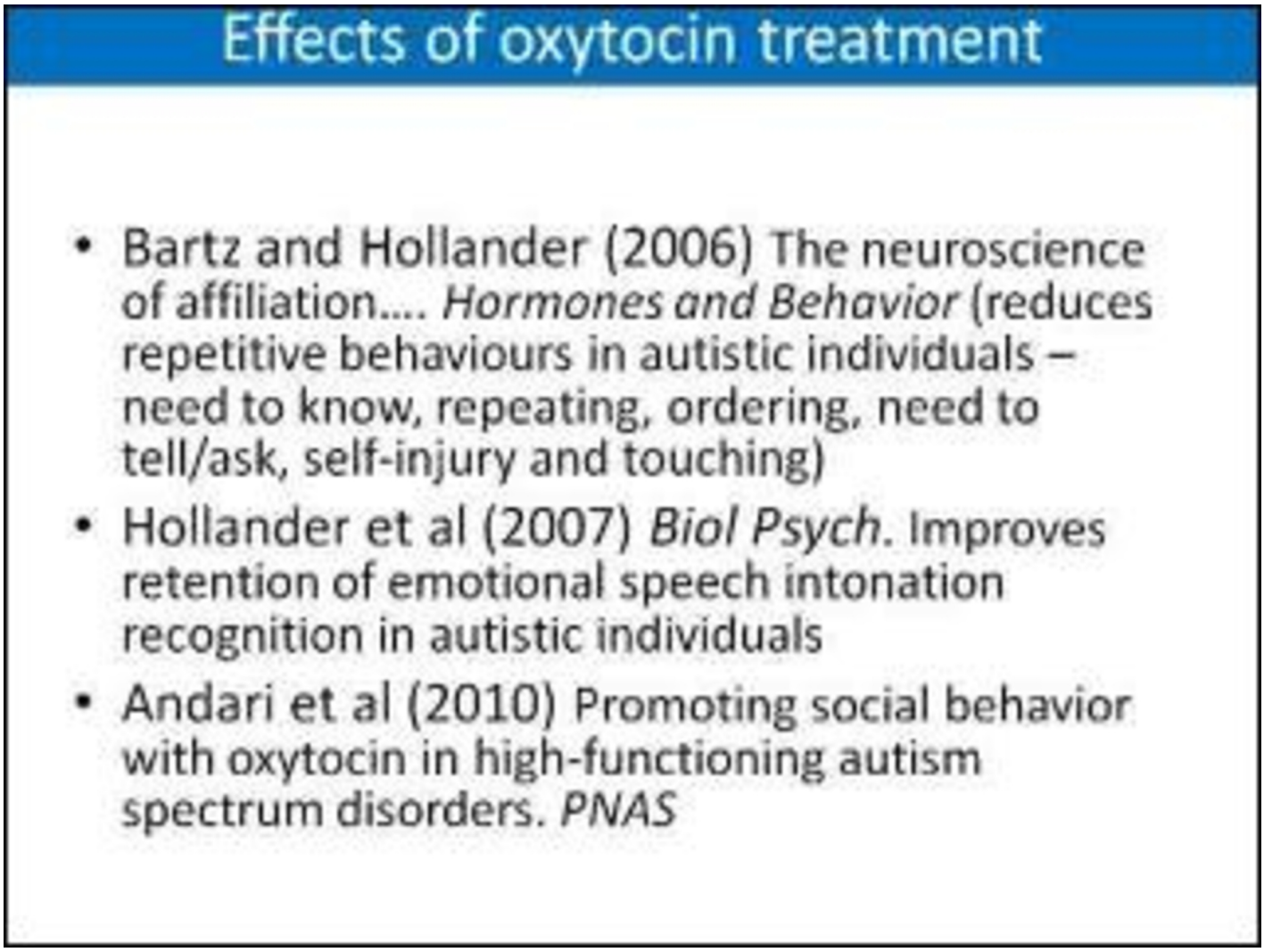

Gresham Lecture, Wednesday 26 January 2011

Repairing and treating damaged or dysfunctional brains

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Good evening, ladies and gentlemen.

This is a fairly ambitious title. I am not going to talk about the whole area or repairing or treating damaged or dysfunctional brains. We have made great advances in neural science in the last decade or so, particularly in diagnostics. I am going to focus particularly within this field on what is currently going on and also what may happen in the near future.

All of us, as neuroscientists, face some enormous societal problems. One of them, you might say, is the creation of a more pro-social or happy brain, and the reason for that is that 1/4 of us will suffer, at some stage during our lives, from clinical depression; 1/10 from some form of social anxiety disorder or social phobia; 1/100 from schizophrenia; approximately 1/200 from various autism spectrum disorders; and in terms of actual damaged brains, dementia, which is primarily, but not exclusively, caused by Alzheimer's disease; vascular disease; and other areas also. This is a problem that is challenging health services across the world as the population ages.

You can see from these figures that problems of senile dementia are only about 1 in 60 at age 60 years old. That increases to 1 in 20 by 70, 1 in 10 by 80, and a staggering 1 in 3 by 90. These are individuals that often need a huge amount of care. Parkinson's disease is around 1 in 500. As I say, the major neurodegenerative disorder is clearly Alzheimer's. There is also traumatic brain injury. About 1 in 50 of us will suffer from some form of traumatic brain injury, and about 1 in 300 individuals have blindness from one cause or another.

This is not my calculation, but somebody decided to come up with how many people on the planet have some form of mental disorder, and they came up with an approximate figure of 2 billion. So, neuroscientists have quite a challenge really in trying to help treat people in this situation.

So the focus of what I will talk about today is not everything – clearly, I could not possibly cover it all in an hour. I am going to particularly look at an area where I have been doing some work recently on effective disorders, and then of course, the big one, neurodegenerative disorders, and, finally, on some advances in restoration of sight and hearing and also damaged limbs in amputees. So the focus is going to be on current strategies and likely developments in the next five to 10 years.

My last talk, in March, which is entitled "Future Brain", will start to explore the science fiction, verging on science fact - the sort of areas that may advance in the next 50 years or so. I want to try and keep our feet on the ground and not try to promise things to you that are actually not going to occur in your lifetime.

As far as the progress in the treatment of effective disorders is concerned, I will, to some extent, touch on treatments which are important for depression, which is obviously the major one, schizophrenia, social anxiety, and also autism.

It probably does not come as a great surprise to you that, in the USA, for example, 28 million people take some form of antidepressants. I remember, when I gave a lecture at Gresham a few years ago on depression, I actually pointed out that traces of Prozac had been found in the water in the UK. It is at that sort of level that people are taking it. It is not dangerous to people, but you can actually detect levels of Prozac in drinking water.

It is a massive depression highway, the road to hell, with a huge number of rather confusing drugs that are available and used, although in fact, to a large extent, they do pretty much the same thing.

This is data that has just come out for Scotland, mainly because it is data that I could actually use to illustrate the point that the number of prescriptions for all the major sort of antidepressants, ranging from the SSRIs, the older drugs, the tricyclics, and various others, are gradually increasing, to quite an extent. In fact, this led Scotland to even debate the point about whether they should be trying to encourage alternatives to drugs because the problems were increasing and drugs were increasing, but really, the sort of ability to deal with depression was not necessarily going hand-in-hand with the use of drugs. I am sure most of you will know that antidepressants have a variety of side effects, as indeed the majority of drugs do, and these can be fairly mild, but they can also be quite severe.

Has everyone heard of electroconvulsive shock therapy? It is a very old way of treating depression. It involves giving people shocks, under anaesthesia, and it had a very bad sort of PR because people were reporting having migraines afterwards. It is done a lot better now. However, electroconvulsive shock therapy is actually more successful at treating depression than drugs. We have not advanced that much! These are two major sort of meta-reviews in both the UK and the USA that were published some time ago, and approximately – this is the other really important take home message – you can see that these treatments never really do much better than provide relief for about half of the people being treated for severe depression. So there are a large number of people who do not respond terribly well to drugs, or at least not to the first few regimes with them. Across these different studies in this one review, electroconvulsive shock therapy was actually more effective than all of the

drugs. It is an interesting point. I am not saying we necessarily ought to completely change to electroconvulsive shock. The important thing is to point out that we have not really made such huge advances in the last few decades in treating depression using drugs.

Of course, there are other non-drug approaches, which are showing great promise that I must mention. Very often, they are even more effective when they are given in conjunction with drug therapies, particularly, for example, cognitive behaviour therapy. This has the advantage that it teaches the person to deal with their distorted perceptions and to help change and discover ways themselves of actually dealing with them. So, as such, when it is effective, it tends to keep people out of depression for a longer time, as opposed to the drugs, which, by themselves, may alleviate the symptoms, but not necessarily deal with the underlying problem. So this has been quite an effective approach which is used more extensively now.

A more extreme technique, which is being used more regularly in a number of contexts - and I will come back to this when we talk about Parkinson's disease later on – is brain stimulation of various forms. It is effectively a far more sophisticated version of electroconvulsive therapy. It is much more targeted and aims to relieve depression by particularly targeting brain regions that promote positive feelings.

Transcranial magnetic stimulation using magnetic pulses to stimulate localised areas of the brain is the least invasive method. Particularly, one of the major targets for this has been areas of the frontal cortex, which is part of the brain reward system. There have been mixed successes, but recently, there have been some papers showing some good effects on people who have drug-resistant forms of depression, and as you can see, it is relatively non-invasive. Here is a guy, Thomas Schlaepfer working in the University of Bonne.

However, there are individuals who do not seem to respond to anything, and there is at least some promise of relief for them, which is a much more drastic and obviously a much more expensive procedure – it could cost $100,000 to do this kind of operation. Permanent electrodes are implanted into areas of the brain which have been discovered to be important for controlling depression symptoms, and these are externalised into a stimulator which hangs on the patient's chest. There have been some very positive results reported from this, admittedly quite extreme, technique.

Although, it is often referred to as "wire-heading", it was interesting that, at a major neuroscience congress in 2005, even the Dalai Lama admitted that, if it was possible to become free of negative emotions by having an electrode implanted in your brain, but without actually impairing intelligence, then he would be the first patient. I am not sure how many of you would choose that surgery. It seems extreme, but of course, when you are suffering from a chronic, debilitating disorder, you will take it, if it works.

One of the areas that I have been working on is the use of what are loosely termed as prosocial peptides and their potential future therapeutic potential. At the minute, there is a limited amount of clinical application of this, but there does seem to be a great potential for it over the next decade, which is one of the reasons I shall spend a little time on it.

Many of you will have heard of agents known as empathogens or entactogens – the classic ones of these are Ecstasy or Adam or GHB – which are addictive drugs and they are not agents that you would want people to be taking routinely. However, they do have an important effect of making individuals feel a lot more positive towards other people. They are highly prosocial and 'touchy-feely' as well. Humans and a large number of other species have naturally occurring prosocial peptides – especially vasopressin and oxytocin, about which I shall talk today.

Just to remind you - perhaps those of you who have not immediately clicked what oxytocin is – it was discovered 104 years ago in London, by Sir Henry Dale. It is from the Greek, meaning sudden delivery, and it is the neuropeptide which, when released from the pituitary into the blood, causes uterine contractions during labour, and if you want to speed labour up, you give a pregnant woman an oxytocin drip. This is the simple diagram showing the well-known aspects of oxytocin being released from the posterior pituitary and causing contraction of the muscles in the uterus and also milk ejection from the breast. However, it is also released within the brain, and this was in fact the area that I first started working on, using sheep as a model back in 1983/4.
In this case, the animal-based research has led to it finally becoming looked at as a very positive and important new therapeutic agent in humans, although it has taken a while.

I was working on how pregnant sheep became maternal when they gave birth, and also how they formed these very strong selective bonds with their lambs. We found that oxytocin was released in their brains when they gave birth, and also during suckling, back in 1986, and the next year, we actually found that a simple infusion of oxytocin directly into the cerebral ventricular system of the brain would stimulate both maternal care and these all-important mother-infant bonds, within 30 seconds. It is a very powerful prosocial agent.

It was also found, in other species, to facilitate social recognition – animals were better able to recognise one another. I will not talk too much about this, but it is a potentially exciting area, though no one seems to want to take it into humans. In animals at least, a number of studies in the 1980s showed that it actually helps improve tolerance to heroin withdrawal. It actually also reduces food intake.

A large number of studies on monogamous prairie voles, one of the few mammalian species that actually form long-term partner bonds, showed that it is released during sex between voles and when it is released, it actually

is responsible for promoting these partner monogamous bonds. There is a different receptor distribution in different species of vole that are either social or not social in their general lifestyle. To put it in a nutshell, the big difference is that the receptors for this peptide in social species are much more densely expressed in these all-important dopaminergic brain reward centres that we are often trying to target when we are trying to make people feel happier and better.

In the mouse, particularly with the advent of being able to obviously manipulate oxytocin and the oxytocin receptor genes in mouse models, it has been shown to be a very important anxiolytic that reduces anxiety and aggression in general, although it actually increases maternal aggression - defence of the young. It appears to be important for social but not non-social recognition, and we know that most of the social recognition actions in animals are via a very important structure in the brain, the amygdala, which controls emotion. It took until the mid-1990s, although there were a few studies earlier than that, for people to start looking at what oxytocin might be doing in humans, and since then, it has exploded exponentially, especially in the last decade.

We showed, very early on, that you cannot simply give someone a tablet with oxytocin or give them an intravenous or intramuscular injection of oxytocin because it does not cross the blood brain barrier very easily, and so you have to find another way of administering it, if you want to get it into the brain as opposed to the rest of the body. Of course, we have known for many years, and drug addicts would tell you this immediately, that a great way of getting things directly into the brain is via the intranasal route – spraying it up the nose. This is because the blood-brain barrier is very weak at the back of the nose. In case I forget to tell you later on, because actually nobody has yet really picked this up in humans, recent animal studies have shown not only can you get substances into the brain that do not normally cross the blood brain barrier this way, you can even get cells into the brain, and that includes stem cells, so it may actually be a way of getting stem cells fro regenerative medicine type therapies into the brain in future, in a relatively non-invasive way. I say that because I am going to talk about stem cells later on.

Now, I will now summarise here a huge amount of work using this intranasal spray approach, often in conjunction with brain imaging as well. This has shown very positively that it increases or facilitates social bonds in humans; trust and generosity, at least in a financial context because that is the only way we can usually measure these things; responses to face expressions; memory for faces; it enhances particularly positive social memories; and interestingly enough, it seems to help you forget negative ones; I told you it was an anxiolytic in animals – it also seems to quite potently reduce psychosocial stress.

Now, one of the things missing from this, when I started working with a clinician in Germany as a psychiatrist, was whether oxytocin really is an empathogen. As I say, there has been animal work showing that, for example, Ecstasy, at least in animals, produces its prosocial effects via modulating oxytocin, so there is a link there, but no one had actually shown whether it can facilitate empathy in humans. Also, although we know it helps with helping you recognise other people and remember them, we did not know whether it had any wider learning implications. We wanted to know whether, if you learnt things where the social reinforcement was concerned, you learnt them better when you were treated with oxytocin. This was important because this might also have an important aspect in the therapeutic side because, very often, a problem with treating a patient with depression is you cannot communicate with them or get them to learn things.

Therefore, we carried out a study, which was published in the spring of last year. It is very difficult to measure empathy, but we used a test that had also been validated on autism spectrum disorder individuals, for example, to show that they had deficits in certain tasks. You see a selection of positive or negative valences of strong emotions and not just with the face. It is a fairly complicated picture, with an individual expressing a range of strong positive or negative emotions. Each of the images, you see three times, within a randomised sequence, and you have to respond to them in different ways. So, in the first case, if we are looking at what we call cognitive empathy - the ability to know what emotion somebody else you are looking at is experiencing, not necessarily to be feeling in any way what they are feeling - they simply have to identify, out of four possibilities, which emotion the person is expressing.

Then we have the two which I think most of you would probably associate more with empathy as we tend to use it in common parlance. The first of these is a direct measurement of emotional empathy – the person is asked to rate, on a scale of one to nine, how much they feel for the person in this picture. Finally, there is also an indirect element of measurement of emotional empathy, and here, the person is asked how much the picture arouses them. It is an imperfect test, but it is one that is a fairly common approach to measuring empathy using questionnaires.

In a study using young German men aged just over 25 or 26, we gave 24 of them either the nasal spray with oxytocin or a placebo, and we gave them this test. There is no effect whatsoever on the cognitive empathy components, so I will not show you that, but all for aspects of the emotional empathy, whether direct or indirect, and whether you are using negative or positive valence pictures, there is a dramatic increase in the intensity ratings of empathy in these individuals. It does not give you euphoria so they cannot guess whether they have actually had oxytocin or the placebo.

To validate this test, because we were looking at another group of, in this case, females, we also compared them with the control male subjects in this study, and you can see there is the expected major sex difference, where females are far more emotional empathic than males, but again, there is no difference between males and

females on the cognitive empathy score. What oxytocin did with the male population in the study was effectively to raise the emotional empathy scores in men up to the level normally seen in women who do not have treatment. At this time, we do not know whether giving the treatment to women will increase their emotional empathy even further. It probably will, but it will not be quite as dramatic as this.

I will now move on to the other question, which was whether oxytocin can facilitate learning when there is some kind of social feedback. Here, we used a very difficult task, where individuals have to learn which of a series of random three-digit numbers belong to category A or category B. They are random, as I say, and the only way you can learn - this is through a series of trials – is through feedback given by faces. If you get it right, you get a smiling face; if you get it wrong, you get an angry face. Or, alternatively, you have a non-social version of this, where you just simply have the black spot changing to a green one or a red – green for right and red for wrong.

This is a very simplified result from it, but it shows two things. With the placebo-treated men, both of the face stimuli actually provide - it seems small, but it is actually highly significant – a better learning curve for the task, compared to the non-social reward. So this is actually the first study we are aware of that has shown something that has been talked about and predicted for a long time; you learn things better when you receive social feedback than in other contexts where you do not. Oxytocin – remember these are male subjects – hugely increased the speed and level of learning when the female face was giving feedback, so perhaps this is a great way to get men to learn much more from women. I will not say any more than that!

Now, there has been a huge amount of work done on this, and we have done a lot, on animals, and so I am saying how we think it works for you. We think that it promotes feelings of attachment, trust and empathy, in both sexes, and it probably does that because we know, from animal studies, that it actually releases this all-important reward transmitter, dopamine, in the brain. We are currently about to start a study in Germany where we are going to be looking, using imagining and PET scanning, at the effects of oxytocin on altering one of the one of the important dopamine receptors, the D2 receptor, in one of these reward areas of the brain, to try and prove that that is the case. It is also interesting that a number of psycho-active drugs target, in fact, or antagonise the D2 receptor, so it may not actually be a great thing to do because you are effectively preventing oxytocin released under normal circumstances from promoting feelings of attachment, trust and empathy. We have yet to show this, but that is the prediction.

It also will reduce anxiety in social contexts, so it could be a really good agent for, for example, reducing social anxiety. It is almost certainly doing this via another set of transmitters in the brain, serotonin, which is often the one that is targeted by SSRIs, for example, like Prozac, and one of the major inhibitory transmitters in the brain, GABA. It also appears to be helping us focus attention on and attraction to social cues and increases protective behaviours. We think that this is via the peptide actually selectively modulating another key transmitter in the brain, noradrenaline. We would like to try to understand far better, again, hopefully using primarily human studies, how oxytocin is modulating these diffuse classical transmitters. It has been used in a clinical context at the moment with regards to autism spectrum disorders, although it is still very early days.

A large number of studies have shown that there are variants of the oxytocin receptor that are significantly associated with autism, but that is true of a number of other genes. However, it does also seem to be the case, both with the oxytocin receptor and one of the vasopressin receptors. These are the particular areas of the gene that are known to vary both in autism, but also, in fact, in individuals who have rather poor social skills in various tasks.

Most recently, although I cannot explain this in enormous detail, one of the things that we are always interested in is how experience can permanently alter somebody's behaviour, and in this case, we are talking about someone's social responsivity. One of the ways that this modification can happen, in us and in other species, is when there is so-called epigenetic modification of the expression of a gene. We actually know, interestingly, that the oxytocin receptor gene has what is called a CpG island in its promoter area, which is one of the areas where you have epigenetic marks which can attract methylation which alters the ability of the gene to be expressed, and that is then passed on from cell to cell within the individual's lifetime. So, once you have had a down-regulation of the receptor through this epigenetic modification, it can last for the remainder of your life.

Interestingly, a recent study published towards the end of 2009, has shown that in a family of autistic individuals that there are increased levels of methylation in this important area of the oxytocin receptor, and, there are a number of regions of it which are apparently affected. They also looked at it both in brain tissue and in blood, in a range of autistic individuals, and they showed, in the temporal cortex - the area of the brain which I talked about before that is important for face recognition and also face emotion recognition - that in autistic individuals, there is indeed, as predicted, a down-regulation of the oxytocin receptor. This means that there is less oxytocin receptor being expressed as a result of these presumably experience-dependent modifications of the oxytocin receptor through the epigenetic route.

As far as effects of oxytocin treatment are concerned, the first study was pretty bad actually. In fact, it did not even give oxytocin intranasally – it gave it peripherally. Nevertheless, they reported, in autistic individuals, that there was a reduction in the repetitive behaviour aspect of autism syndrome – which means the need to know, repeat, order, tell, ask, self-injure, touch and other things. They then looked at the brain and found that it actually improved retention of emotional speech intonation and recognition in autistic individuals. However, the study that really got everybody sitting up was published just last year by a French group. They showed, in high-functioning

autism individuals, that there was a highly significant increase in their social behaviour when they were playing role-playing games which had a social component.

I am hoping to be involved in a study in Cambridge looking in more detail at how oxytocin might be used in the context of helping in the treatment of autistic individuals. By itself, it is not going to work – it needs to be used with other things, but it does seem to have at least some effect in promoting prosocial behaviours and social responsivity, which is what you want to do.

It has also been looked at in the context of schizophrenia. Oxytocin was first suggested to have antipsychotic properties in 1974. There are abnormalities in oxytocin levels released in the blood, and also responses to trust, in schizophrenics. Again, about six months ago, there was the first major study – only on 19 patients, but still very encouraging – where the effects of a three-week treatment with intranasal oxytocin showed that it actually improves positive symptoms, in schizophrenic patients. Importantly, these patients are already being treated with antipsychotics, so you are actually improving over what current antipsychotics are able to produce in these individuals. These are still early days, but it does seem potentially to have application in treatment of schizophrenia as well.

Although a major study has yet to come out, we are expecting that it will have a very potentially important role in the treatment of social anxiety disorder. We know this particularly because one of the things that it does is suppress the reactivity of this amygdala region of the brain which is responding to the emotional faces. It is turning down again, so you do not respond quite as negatively to other people, which is clearly one of the major aspects of social anxiety disorder.

We know that there are changes in oxytocin in depression, but there have not really been any good studies looking at whether it could help in the treatment of depression, possibly particularly in association with cognitive behaviour therapy. There have been associations with oxytocin changes in borderline personality disorder.

I know of a few studies going on at this minute, looking at the application of oxytocin nasal sprays to, post-traumatic stress disorder. The reason it is being used in that context is that it seems to, as I mentioned earlier on, from animal studies, reduce responses to negative affect stimulation - it helps you forget the bad things and remember the good things. It may also be helpful in helping people to come off drugs, although, again, there is yet to be a study launched on this.

As I say, it is not a miracle cure. You do not take nasal spray with oxytocin and suddenly feel great. It is likely to be, in the therapeutic context, most useful as an adjunct treatment to other kinds of treatment, particularly behavioural ones, but it has great promise. I think we will find that this is used increasingly in the clinic over the next 10 years.

We are now going to move on to the big one: progress in the treatment of neurodegenerative disorders. I shall focus just on Alzheimer's and Parkinson's. Just to remind you, about 60% of dementia is associated with Alzheimer's, about 30% stroke/vascular dementia, and "others" around 10%. In terms of the predictions in levels of Alzheimer's disease worldwide, we are talking about potentially 35.6 million in 2009, rising to almost three times that number in 2050, so it is a very serious problem for us, and we need to find ways of at least alleviating the symptoms, if not entirely being able to prevent them occurring at all.

I will start with Parkinson's, perhaps because there have been the most advances made in this compared to Alzheimer's, because Alzheimer's is a much more general destruction of the brain. Parkinson's is fairly restricted and therefore, in theory, should be easier to treat. It is a result of progressive degeneration of dopaminergic neurons that are very important for the control of movement, among other things, in the Substantia Nigra. You do not normally see someone experiencing significant symptoms of Parkinson's until nearly 80% of the dopamine cells in this region are actually destroyed, so it takes quite some time for the destruction of this area to reveal itself in terms of behaviour.

Unsurprisingly, because it involves dopaminergic neurons, the treatments that have developed right from the start have all been to boost dopamine levels. You can give dopamine in artificial forms; by itself – a very common treatment – Levodopa; as dopamine agonists, or you can target other agents which are important for the breakdown of dopamine. Overall, these treatments do work, but very often, eventually the body become resistant to them, and they have other side effects, so you end up with them, in many cases, after many years anyway, ceasing to be as effective. That has led to consideration of somewhat more sophisticated, if you like, approaches, to try and deal with or repair the damage in the Substantia Nigra, or at least to try to alleviate the symptoms, the shakes and tremors, which of course cause problems with everyday life.

One of the most successful of these came out of research which was done on monkeys - it would not have come out if it had not have been done on monkeys. One of the things Parkinson's disease does is to weaken the control of the sub-thalamic nucleus and that is what leads to the tremors. If you implant electrodes into this region and stimulate them optimally – again, the patient is carrying the stimulator on her chest – you can totally control the tremor symptoms. If you look on YouTube, there are lots and lots of examples of this. It is quite remarkable seeing the effects of turning on and turning off the stimulator. Of course, it has given back a really great quality of life to individuals who were not responding to drugs. It is an extreme way of doing it, but it is very effective.

There are other approaches. There have been a number of attempts to use foetal transplants – this involves transplanting parts of this damaged part of the brain from the foetus into the Parkinson's patient and hoping that the graft or the transplant will regenerate the dopamine neurons and result in the person getting back their control of function. Quite a few studies have done this and it does seem to have some effect, although results are variable. There was considerable concern about whether this approach would really fall because while you could implant these cells, perhaps they might also be subject to the Parkinson's pathology and therefore they would be killed and not be able to stick around long enough to actually have any positive effects. One study with humans has recently shown that these cells are still healthy 4 to 12 years later, although there is also one study that did report some problems over time. It is a pretty extreme approach and I will not promise that it is amazingly effective, but it does seem to have some benefit.

Another approach is being developed now by Neurologix and its phase two trial has been completed. It is working with the sub-thalamic nucleus again, but rather than stimulating it electrically, in this case, they are actually introducing a virus with a gene that is promoting the release of an important substance that controls the inhibitory transmitter, glutamic acid decarboxylase. The idea is that through introducing this into the brain, you effectively fulfil the same function as the stimulating electrode: you increase the activity of the sub-thalamic nucleus, but you do not have to keep turning off and on a stimulating electrode. This seems to have had some success but it is still way off potentially being something that will be available.

Another approach is the all-important much-talked about stem cell therapy and there are a number of different approaches for using stem cells. I do not have time to go into them, but this is just an example that is being used. You take stem cells from the patient, perhaps from the bone marrow, isolate them, amplify them, and then differentiate them, in this case, into dopaminergic neurons. They are the patient's own stem cells, so you are not going to get any rejection, and then you inject the stem cells into the damaged area of the brain. That is the theory! There are a number of clinical trials going on, using variants of this, but you should be aware, if you are a Parkinson's patient or suffer from a number of disorders, that these stem cell therapies, or versions of them, are already available in a number of clinics, not in the UK. The closest one, the XCell Centre in Germany is very big. .

I only put this up because this has not had any clinical trials completed on it. They have gone straight ahead and are treating patients. They claim all sorts of things, but they are not actually quantifying it and giving us any kind of useful feedback as to how effective these treatments are. I would suggest that the buyer beware. These treatments cost between 10,000 and 20,000 Euros but, for those of you who understand the legal aspects of medicine, the reason that you cannot get these kind of clinics in the UK is because stem cell therapy is regarded as a medicine in the UK and therefore it is regulated in the same way other medicines are, which means you have to go through clinical trials. In Europe, and indeed in other parts of the world, which have allowed these centres to grow up there are loopholes around this. Hundreds of Britons are going over to this clinic every year, to have treatment, but we really do not know the success rate and whether it is worth the money. We need more clinical trials, and they are going on, but it is a slow business. That is why the clinical trials will probably take 10 years before, if they are successful, they become available to us.

Moving on to Alzheimer's, again, there is a very dramatic degenerative change in the brain. In this case, it is large amounts of the brain. This an advanced Alzheimer's brain, completely shrunk due to the massive amount of cell death compared to a healthy brain, and this is primarily caused by the development or growth of plaques and what are called tangles, which pretty much strangle neurons and kill them, all over the brain, but particularly in areas of the brain that are controlling cognitive function. It particularly affects the cholinergic system, for example, in the brain, which is very important for cognitive function. We have begun to understand quite a lot about the genes that are contributing to the formation of these plaques and tangles, although, as yet, the association between them and pathology is still not quite as strong as we would like it. You will notice, at the minute, that primarily therapies are trying to improve cognitive function, rather than being able to, in some way, either stop it happening or to reduce the plaques and tangles significantly or to promote regrowth of damaged regions, although there is some work being done which is targeting trying to restore the damage.

The drugs that are used are of varying degrees of success. They tend to target the acetylcholine system, which is considerably degraded in an Alzheimer's brain; you boost acetylcholine levels by using cholinesterase inhibitors. Aricept of course is the major drug used for this. There is another way of doing it, which is to boost another important, in this case, receptor, called the glutamate receptor, the NMDA receptor, using drugs, and the classic one for these are actually the same drug, Nemender and Memantine.

There are a number of others that have been mooted as cognitive enhancers in various contexts, including Provigil, Adderall, Ritalin, which you have probably heard of in the context of treatment of ADHD. It is potentially becoming a drug of abuse for people for leisure. There is another group, which have been developed for some time, another part of the glutamate signalling system, which is important for learning, so-called Ampakines. One that I have been working on, and some other people have is D-cycloserine, which is actually an antibiotic. It is used in the treatment of tuberculosis, but it actually has another property- it is an NMDA receptor agonist, glutamate receptor agonist. We published a study in the middle of last year, in Biological Psychiatry. You can take it orally, and it is just one dose. These are normal, young, male Germans. You take the pill, and you do that task I have already shown, but in this case, not the social bit, just the feedback with the green and red lights. One oral dose of cycloserine actually enhances cognitive performance in this task. It also increases the activity of one of

the all-important regions for learning and memory, the hippocampus, which is also the one which is particularly affected in neurodegenerative disorders like Alzheimer's.

It is not yet being used in the context of treatment of Alzheimer's, but it is already licensed for treatment for tuberculosis, so it might not be that difficult to actually look at whether it has beneficial effects in people with neurodegenerative disorders although that study has yet to be done.

There is another promising area in treatment of Alzheimer's disease. As you can probably expect, when you get all this killing of neurons, you also get a huge amount of inflammation as well, and, for a while, it was being mooted that the use of anti-inflammatory drugs, particularly the non-steroidal ones, the Ibuprofens and Aspirins and so forth, had beneficial effects in Alzheimer's patients. More recent studies have really concluded that, at best, it probably delays the onset, or helps to delay the onset, of dementia, and this is the most recent study that's come out.

However, there are also some genes associated with inflammatory diseases, such as rheumatism, for example, which appear to be associated with, or helpful in targeting and treatment of Alzheimer's. One of these is the so-called tumour necrosis factor, which is the one you target with drugs when you treat rheumatism. There have been a couple of recent studies showing rapid cognitive improvement with Alzheimer's disease following treatment with anti-TNF drugs. Again, it is still early days, but it seems to be another approach to studying or helping control the symptoms of Alzheimer's.

As far as gene therapy is concerned, there are clinical trials underway. In this case, they are trying to help regrowth in damaged areas, so they are targeting the production of a factor that helps this endogenous nerve growth factor. Here, there are two studies that have just gone into phase two in the US where they are recruiting Alzheimer's patients to undergo this gene therapy. The patients are given viruses in a way that can actually promote the release of nerve growth factor.

However, it must be emphasised that you can still help yourself. While there are advances going on, they will take a while to develop, so there are things you can do now, such as diet and exercise. You have the same risk factors in Alzheimer's as you do in cardiovascular disease, so, a good diet – the Mediterranean type diet, for example – and exercise have been shown, in a number of studies, to help with Alzheimer's. The more different types of exercises and the number of exercise sessions lasting longer than 20 minutes, all have a good association with not having cognitive impairment.

There is also this concept of 'use it and delay the onset of dementia'. This is because of the "cognitive reserve" hypothesis, as it is called. The idea is, if you use your brain a lot, you develop more cells, particularly in areas like the hippocampus. All these neurodegenerative disorders – Parkinson's and Alzheimer's – do not start to produce symptoms until there is quite a large amount of cell loss. So you can imagine, therefore, if your lifestyle has promoted an increased number of neurons in key areas that are involved in, for example, cognitive function, it will take longer for the neurodegenerative disorder to actually create any negative symptoms.

A number of studies have claimed this. One group has generated this life experience quotient, which tries to assess how much you use your brain, and they have shown – we know that Alzheimer's, particularly, shrinks the hippocampus, which is this all-important region of the brain – that the amount of hippocampal volume is nicely positively correlated with the score on this particular test.

They did a study which they just published a few years ago, where they looked at 65 year olds and followed them over three years. They measured the hippocampal volume during these three years. Those that had, right from the beginning, a high lifestyle experience quotient showed very little decrease in the volume of their hippocampus over this three year period, whereas those that started off with a low score experienced a much more significant decrease. It was trying to persuade you really that it is good to try and use your brain and promote growth of your hippocampus in order to protect you from at least getting Alzheimer's disease early. For those of you who are interested, this particular questionnaire is actually available on the web if you want to take it.

I am going to finish just on some interesting areas. To some extent, it is peripheral because we are talking about sensory organs here rather than the brain at this particular point in time, but there are some really interesting advances in providing hearing for the deaf, vision for the blind, and also artificial limbs for amputees.

I will give you this one, which I think probably many of you have heard - a cochlea implant. Where there is peripheral damage, you can actually implant large numbers of electrodes onto the auditory nerves in the inner ear, link them to a digital device which translates sounds, and these will then stimulate the auditory nerve. The individual can effectively be trained to hear again, to some extent, as a result of this. If you like, it is almost a brain-machine interface – you are using silicon technology and actually translating that into a sort of interface with biology through the use of electrodes.

The same approach is being used to try to help restore sight to individuals who have damaged retinas, either through age or as a result of, for example, Type 2 diabetes. Here, large scale electrode arrays are implanted into the retina, and depending upon how many electrodes are implanted, a degree of vision can be restored.

This is how these implants look in the macula of the retina. This is one of these arrays. This individual, with these

implanted arrays can now discriminate between for example, an apple and a banana.

Perhaps even more exciting, as it is fairly extreme to put electrodes into the damaged retina, it would be great if you could actually replace the damaged cells. There are now two major pharmaceutical companies who are committed to developing the use of stem cell therapies. In animal studies they have been shown to be very effective in at least restoring a degree of vision, and early clinical trials in humans have also shown that it is an interesting or important way of being able to restore retinal function. AstraZeneca has now joined with University College London to find the same kind of approach using embryonic stem cells. This could ultimately be a half-hour operation, where you get an injection of these stem cells into the back of the eye, and, over a period of time, you will get restoration of some degree at least of vision.

I hesitate to show a patient from the XCell Centre, but this therapy is available in the XCell Centre already, and this is a patient who claims that that was his vision before the stem cells in the retina, and that was what he was able to discriminate after.

Finally, I should not sort of avoid talking about the other sort of brain/machine interface areas, which are neural prosthesis in amputees. Clearly, it would be great if you could control artificial limbs using your own nervous system, and that is now really being substantially developed with the ability to link in robotic devices with the patient's nervous system, so that they can actually control these complex devices, both arms and legs. This is a recent case, where this woman has the nerves linked to this arm here, which she is learning to control quite effectively in a number of complex movements. This is another area where there are advances helping to link the brain to control devices so we can get restoration of movement.

I should perhaps also mention that there is, at the minute, a big clinical trial going on for the use of stem cells, for example, for spinal damage as well, and that is another area that a lot of people are really very interested in. As yet, it is still quite a long way off but it is another area of important research that could help with movement control.

So, in summary, we are making considerable progress in identifying molecular targets for the potential treatment of brain disorders, but we still have a long way to go. Therapeutic advances have been made, particularly recently with the use of electrical brain stimulation approaches. Gene therapy is also beginning to come forward and have promise, although they do require the use of viruses because it is the only way you can get genes into cells and there is always a slight downside to the use of viruses.

Stem cell therapies also have potential promise, although, to a large extent, one could claim that these may be being damaged by the availability of therapies before we have done the really important clinical trials. That may well damage public and professional confidence in their use, which could obviously delay. There are also big issues, both ethical and also technical, as to whether we should be using embryonic or adult stem cells. I will not go into this, but we do need to have a lot more work really on generating stem cell lines and deciding how to avoid, especially with embryonic cells, possible rejection issues.

Neural prosthetic approaches, as I mentioned at the end, are developing rapidly. Unfortunately, developing new treatments in clinical trials is a slow process which is why these companies that are getting through the legal loopholes to be able to provide potential new treatments today, rather than in five and 10 years when they have been proven have such appeal. However, it will take at least another 5 to 10 years before any of the kind of things that I have been talking about today are available for treatments. Finally, it must always be emphasised that lifestyle choices are still of great importance in helping or avoiding to reduce problems.