Edexcel GCE

Biology

Advanced

Unit 5: Energy, Exercise and Coordination

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Scientific Article for use with Question 8

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Deep brain stimulation

Introduction

1. Deep brain stimulation (DBS) is a surgical treatment involving the implantation of a medical device called a brain pacemaker, which sends electrical impulses to specific parts of the brain. DBS in selected brain regions has provided remarkable therapeutic benefits for otherwise treatment-resistant movement and affective disorders such as chronic pain, Parkinson's disease, tremor and dystonia. Despite the long history of DBS, its underlying principles and mechanisms are still not clear. DBS directly changes brain activity in a controlled manner, its effects are reversible (unlike those of lesioning techniques) and is one of only a few neurosurgical methods that allows blinded studies.

2. DBS was approved as a treatment for essential tremor in 1997, for Parkinson's disease in 2002, and dystonia in 2003. DBS is also routinely used to treat chronic pain and has been used to treat various affective disorders, including major depression. While DBS has proven helpful for some patients, there is a potential for serious complications and side effects.

3. The deep brain stimulation system consists of three components: the implanted pulse generator (IPG), the lead, and the extension. The IPG is a battery-powered neurostimulator encased in a titanium housing, which sends electrical pulses to the brain to interfere with neural activity at the target site. The lead is a coiled wire insulated in polyurethane with four platinum iridium electrodes and is placed in one of three areas of the brain. The lead is connected to the IPG by the extension, an insulated wire that runs from the head, down the side of the neck, behind the ear to the IPG, which is placed subcutaneously below the clavicle or in some cases, the abdomen. The IPG can be calibrated by a neurologist, nurse or trained technician to optimize symptom suppression and control side effects.

4. DBS leads are placed in the brain according to the type of symptoms to be addressed. For non-parkinsonian essential tremor the lead is placed in the ventrointermedial nucleus (VIM) of the thalamus. For dystonia and symptoms associated with Parkinson's disease (rigidity, bradykinesia/akinesia and tremor), the lead may be placed in either the globus pallidus or subthalamic nucleus.

5. All three components are surgically implanted inside the body. Under local anaesthesia, a hole about 14 mm in diameter is drilled in the skull and the electrode is inserted, with feedback from the patient for optimal placement. The installation of the IPG and lead occurs under general anaesthesia. The right side of the brain is stimulated to address symptoms on the left side of the body and vice versa.

6. It has been shown in thalamic slices from mice that DBS causes nearby astrocytes to release adenosine triphosphate (ATP), a precursor to adenosine (through a catabolic process). In turn, adenosine A1 receptor activation depresses excitatory transmission in the thalamus, thus causing an inhibitory effect that mimics ablation or "lesioning".

Parkinson's

7. Parkinson's disease is a neurodegenerative disease whose primary symptoms are tremor, rigidity, bradykinesia and postural instability. DBS does not cure Parkinson's, but it can help manage some of its symptoms and subsequently improve the patient's quality of life. At present, the procedure is used only for patients whose symptoms cannot be adequately controlled with medications, or whose medications have severe side effects. Its direct effect on the physiology of brain cells and neurotransmitters is currently debated, but by sending high frequency electrical impulses into specific areas of the brain it can mitigate symptoms and/or directly diminish the side effects induced by parkinsonian medications, allowing a decrease in medications, or making a medication regimen more tolerable.

8. There are a few sites in the brain that can be targeted to achieve differing results, so each patient must be assessed individually, and a site will be chosen based on their needs. Traditionally, the two most common sites are the subthalamic nucleus (STN) and the globus pallidus interna (GPi), but other sites, such as the caudal zona incerta and the pallidofugal fibres medial to the STN, are being evaluated and showing promise.

9. Research is being conducted to predict the onset of tremors before they occur by monitoring activity in the subthalamic nucleus. The goal is to provide stimulating pulses only when they are needed, to stop any tremors occurring before they start. DBS is approved in the United States by the Food and Drug Administration for the treatment of Parkinson's. DBS carries the risks of major surgery, with a complication rate related to the experience of the surgical team.

10. Julia is only in her mid-thirties but for the last five years she has been suffering from the disabling symptoms of Parkinson's disease. Most sufferers from Parkinson's are much older than Julia. In fact, Parkinson's disease is the most common movement disorder and the second most common neurodegenerative disease, affecting 1% of the population above the age of 65. With the ageing population in the developed world this imposes a heavy burden on society. Many ageing patients can be helped for some years by drugs such as *levadopa* or dopamine agonists. But unfortunately approximately one tenth of them do not respond to this drug.

11. Julia finds things very difficult and the disease has now progressed so far that Julia is in need of full time care. A few years ago there would have been nothing that could have been done for her and she would have had to try to live with the slow, agonising decline of function. But recently, after years of careful animal experimentation, our lab has found that Julia and others with similar symptoms can in fact be helped by deep brain stimulation of a region called *the pedunculopontine nucleus.*

12. The effects are instant and almost magical to a casual observer. After electrodes have been implanted in her brain and connected to a battery in her chest, Julia is suddenly able to walk by herself without hesitation and without falling over. In contrast, these effects are almost immediately reversed when the battery is turned off. After years of suffering, Julia is now able to lead a much more normal life and may even be able to return to work.

Major Depression

13. There is insufficient evidence to support DBS as a therapeutic modality for depression; however, the procedure may be an effective treatment modality in the future. Researchers reported in 2005 that electrical stimulation of a small area of the frontal cortex brought about a "striking and sustained remission" in four out of six patients suffering from major depression. Their symptoms had previously been resistant to medication, psychotherapy and electroconvulsive therapy.

14. Using brain imaging, the researchers had noticed that activity in the subgenual cingulate – the lowest part of a band of tissue that runs along the midline of the brain – seemed to correlate with symptoms of sadness and depression. They implanted electrodes into six patients while they were locally anaesthetised, but alert. While the current was switched on, four of the patients reported feeling a black cloud lifting, and became more alert and interested in their environments. The changes reversed when the current was switched off.

15. The effects of continuous subgenual cingulate stimulation have produced sustained remission from depression in the four patients for six months. When reporting the results, the team did caution that the trial was so small that the findings must be considered only provisional.

16. Another hypothetically interesting site for DBS in depression is the nucleus accumbens, as that region appears to be associated with pleasure and reward mechanisms. A 2007 study reported that experimental use of deep brain stimulation of the nucleus accumbens showed promising results, with patients suffering from profound depression reporting relief from their symptoms.

17. A systematic review of DBS for treatment resistant depression and obsessive – compulsive disorder identified 16 studies, nine for OCD, seven for treatment-resistant depression, and one for both. It found that "about half the patients did show dramatic improvement" and that adverse events were "generally trivial".

Tourette syndrome

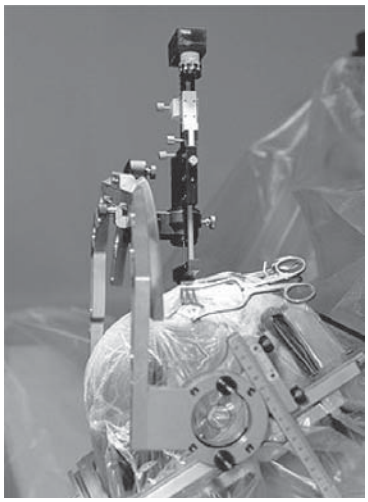
18. Deep brain stimulation has been used experimentally in treating a few patients with severe Tourette syndrome. Despite widely publicized early successes, DBS remains a highly experimental procedure for the treatment of Tourette's, and more study is needed to determine whether long-term benefits outweigh the risk. The procedure is well tolerated, but complications include "short battery life, abrupt symptom worsening upon cessation of stimulation, hypomanic or manic conversion, and the significant time and effort involved in optimizing stimulation parameters". As of 2006, there were five published reports of DBS in patients with TS; all experienced reduction in tics and the disappearance of obsessive-compulsive behaviours. "Only patients with severe, debilitating, and treatment-refractory illness should be considered; while those with severe personality disorders and substance abuse problems should be excluded."

19. There may be serious short- and long-term risks associated with DBS in persons with head and neck tics. The procedure is invasive and expensive, and requires long-term expert care. Benefits for severe Tourette's are not conclusive. Tourette's is more common in paediatric populations, tending to remit in adulthood, so this would not generally be a recommended procedure for use on children. Because diagnosis of Tourette's is made based on a history of symptoms rather than analysis of neurological activity, it may not always be clear how to apply DBS for a particular patient. Due to concern over the use of DBS in the treatment of Tourette syndrome, the Tourette Syndrome Association convened a group of experts to develop recommendations guiding the use and potential clinical trials of DBS for TS.

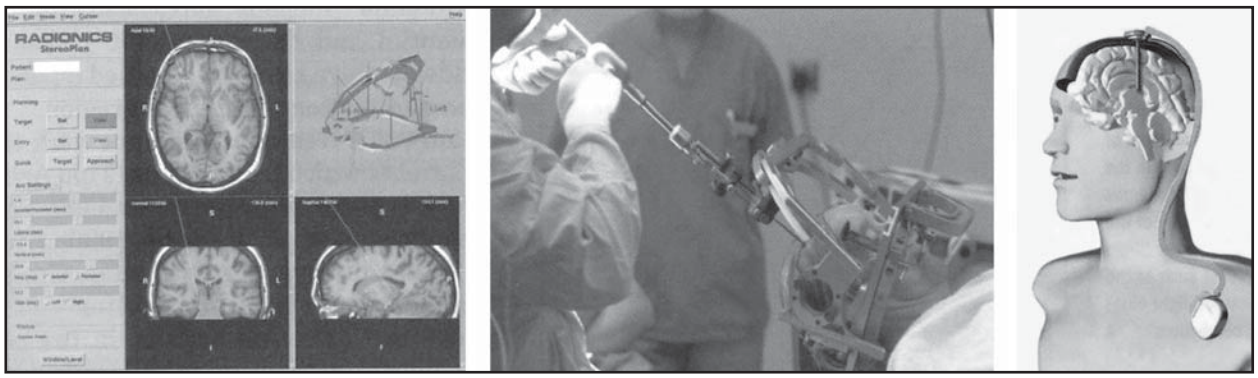
Chronic 'suicide headaches'

20. Much less visually spectacular but equally life-transforming is the use of deep brain stimulation (DBS) in patients suffering from chronic pain such as phantom pain or cluster headache.

21. Jamie is a 45 year old man who, several times a week, would get debilitating, piercing headaches on the left side of his head. The onset of attacks was rapid and lasted for up to three hours. The pain associated with cluster headache is intense and with pain medication mostly ineffective, the disease has become known as 'suicide headache'. In fact, Jamie's current aura of calm belies the suffering that drove him into deep depression and almost to suicide.



22. The precise anatomical information acquired from brain imaging combined with the use of a stereotactic frame allows the neurosurgeon to implant electrodes in almost any part of the brain. The surgery is performed while the patient is awake, so once the electrodes are in place, the neurosurgeon can stimulate them and obtain direct subjective reports on the effects of the stimulation. Jamie was thus fully awake when the team implanted an electrode with four contacts in the hypothalamus in the centre of the brain. This target is based on functional brain imaging experiments of patients suffering from cluster headaches which have shown that the focus of the disease lies in the posterior hypothalamus.



The neurosurgical procedures involved in DBS

The patient is scanned with a stereotactic frame and the neurosurgery is preplanned using stereotactic planning software. The precise positioning of the electrode is performed by perforating the calvarium with a twist drill. The electrode is secured to the skull with a titanium miniplate and the implantable pulse generator is placed in a subcutaneous pectoral pouch. The relative positions of the electrode, lead and a battery within a patient's head and chest are shown above.

23. Jamie had an attack of cluster headache on the operating table which was recorded with the deep brain electrodes. But this was the last cluster headache Jamie had and the deep brain stimulation has subsequently transformed his life.

24. The battery was connected and days later, once his cluster headaches had truly stopped, a long-lasting battery was implanted subcutaneously over Jamie's right breast muscle and connected permanently to the deep brain electrodes. Through a remote control, the frequency, pulse width, and voltage of the stimulation are changed to obtain the best possible parameters for alleviating his cluster headache should it come back. If need be, the electrodes can be removed completely.

25. Jamie is now back to doing the things he enjoys which includes such everyday activities as playing with his grandchildren – without the fear of being cut short by unbearable pain.

Dystonia

26. In 1988, Paula's physical pain started to affect her professional relationships and her career. Her colleagues at the radio station where she worked couldn't understand what was happening to the enthusiastic and vivacious woman they once knew and admired.

27. Paula was in a great deal of pain. She couldn't sit down or walk for more than a few minutes at a time. She tried everything to cope with the disabling pain and disfigurement she later learned was the result of dystonia.

28. Dystonia is a neurological movement disorder that causes involuntary muscle contractions. These contractions force certain parts of the body into abnormal, repetitive, twisting, and sometimes painful movements or postures.

29. Eventually, Paula was forced to quit her job. Embarrassed by her appearance, Paula stopped venturing outside of her home. She became depressed, and worried that she would never again be able to do the things she loved, like playing with her nieces and nephews, working, and travelling.

30. Paula tried everything to cope with the disease. She started regimens of oral medications and injection treatments. At one point, Paula received up to 20 shots of Botox® every few months. At first, these treatments helped stabilize her symptoms, but her situation had "gotten out of control," as she recalls.

31. On the advice of her neurologist, Paula underwent surgery for Medtronic DBS Therapy for Dystonia.

32. After the procedure, Paula spent time reorienting herself to her own body. "I'm still amazed that I can actually pick up objects with my hands," she says. "Before DBS, my body did whatever it wanted. I had no control over it." Today, Paula lives on her own and maintains an active lifestyle. She can cook, swim, exercise and meet friends for dinner – all activities she had to put on hold due to dystonia. "Most people can't believe that I'm the same person," says Paula. "I'm just thrilled to have my life back."

Cerebral Palsy

33. Young cerebral palsy patients, especially the youngest ones, may get relief from dystonia symptoms with deep brain stimulation.

34. Deep brain stimulation, which has shown efficacy for primary dystonias in adults, may have similar effects in children with secondary dystonias resulting from cerebral palsy, although this was a small, ongoing, single-centre study. This study was published as an abstract and presented as a poster at a conference and so the data and conclusions are preliminary until published in a peer-reviewed journal.

35. In this study of six patients ages eight to 26, the therapy resulted in the greatest improvement in dystonia scores for children under 12. "We tend to see the most improvement in their arms," Dr. Marks said. "But none of them have gone from nonambulatory to walking."

36. Deep brain stimulation has been widely used to treat primary dystonias in adults, but is much less often employed for children with secondary dystonias, such as those in cerebral palsy. So to evaluate the efficacy of the therapy in a paediatric population, the researchers conducted a retrospective analysis of all cerebral palsy patients who have undergone deep brain stimulation at Cook Children's Hospital.

37. Between September 2007 and March 2009, seven nonambulatory patients with severe dystonic hypertonia due to cerebral palsy had the implantation surgery and subsequent treatment. All of the patients had been refractory to pharmacological interventions. Patients were followed for six to 12 months.

38. Dr. Marks said all the patients demonstrated improvement by at least one of three rating scale measures, with the greatest improvement in dystonia scores among patients under age 12. "The younger patients do better, probably because the older patients have more fixed orthopaedic impairment," he said.

39. However, none of the patients who'd lost the ability to walk regained it during the first six months of treatment. Dr. Marks noted that the treatment targets only dystonia, not spasticity, which is also a common problem in cerebral palsy patients. L. Verhagen Metman, M.D., of Rush University in Chicago, who presented findings on deep brain stimulation in primary dystonias, some in paediatric patients, said the treatment appeared successful in children with genetic dystonia. However, he said that for children with secondary dystonias, such as those resulting from cerebral palsy, it may not have the same success rate.

40. Both Dr. Marks and Dr. Metman said deep brain stimulation has very few side effects. One paediatric patient in Dr. Metman's study became dysphagic, but the complication resolved in two days. Dr. Metman also noted that more researchers are finding that some dystonic patients become parkinsonian after deep brain stimulation, and he had one patient with this side effect in his study. Still, Dr. Marks said his findings show that younger dystonic cerebral palsy patients will likely have improvements in tonal abnormalities with deep brain stimulation, and that older patients may still benefit from overall tone management.

Tremor

41. Tremor is an involuntary rhythmic repetitive movement, most frequently affecting the upper limbs. It can occur at rest or can be brought on (or exacerbated) by posture or intentional movement. Severe tremor can be disabling because it affects fine-movement coordination.

42. Tremor can be treated by rehabilitation and drug therapy, and early appropriate treatment may minimise functional disability. Anti-tremor drugs reduce the amplitude but not the frequency of tremor, and this does not always translate into functional improvement. Surgery, which often involves ablation of the thalamic nucleus, is usually reserved for patients with severe disabling tremor and functional disability that interferes with activities of daily living, and for tremor that is refractory to the highest tolerated doses of medication.

43. Very few data are available on the use of deep brain stimulation for tremor in multiple sclerosis. Three case series reported significant improvements in tremor secondary to multiple sclerosis at 12–22 months; however, two of these studies found that improvements in tremor did not necessarily correlate with improvements in functional ability.

Other clinical applications

44. In August 2007, Nature reported that scientists in the US had stimulated a 38 year-old man who had been in a minimally conscious state for six years using DBS. The patient initially had increased arousal and sustained eye-opening, as well as rapid bilateral head-turning to voice. After further stimulation, the previously non-verbal patient became capable of naming objects and using objects with his hands – for example, bringing a cup to his mouth. Moreover, he could swallow food and take meals by mouth, meaning he was no longer dependent on a gastrostomy tube.

45. This result follows research carried out over 40 years, which has analysed the effects of deep brain stimulation in the thalamus (and elsewhere) in patients with post-traumatic coma. While this research has shown some potential, deep brain stimulation is not yet a reliable cure for patients in post-traumatic coma. DBS has been used in the treatment of obsessive-compulsive disorder and phantom limb pain. Although the clinical efficacy is not questioned, the mechanisms by which DBS works are still debated.

46. Long-term clinical observation has shown that the mechanism is not due to a progressive lesion, given that interruption of stimulation reverses its effects. Results of DBS in dystonia patients, where positive effects often appear gradually over a period of weeks to months, indicate a role of functional reorganization in at least some cases. The procedure is being tested for effectiveness in patients with severe epilepsy.

A brief history of neuromodulatlon

47. So how does the magic of deep brain stimulation work? However magical it may look, the alleviation of Julia's, Jamie's and Paula's symptoms is obviously not the product of magic but of careful scientific experimentation.

48. It has been known for some time that electricity plays an important role in the body. Benjamin Franklin noted in 1774 that static electricity can lead to muscle contraction. Even before that, in 15 AD, Scribonius noted the alleviation of gout pain in a man who stepped on a torpedo fish, one of the electric fish species.

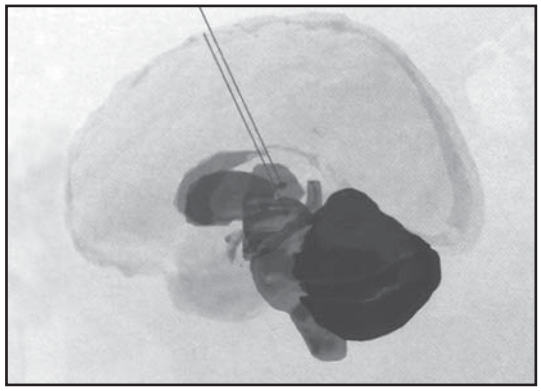
49. In fact, muscle movement is the *final common pathway* of these electrical discharges as pointed out by the Nobel Prize-winner Charles Sherrington who in 1906 wrote that "...to move things is all mankind can do; ... for such the sole executant is muscle, whether in whispering a syllable or in felling a forest".

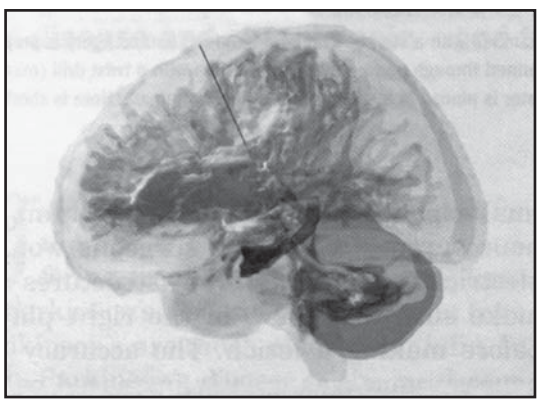
50. The muscles are ultimately controlled by the brain – but it was not until 1870 that Fritsch and Hitzig demonstrated this principle by controlling limb movements in a dog with direct stimulation of its motor cortex. This insight soon found its way into animal experiments and finally into human neurosurgery where the surgeons would electrically stimulate brain structures to make sure they were in the right place before making a lesion. The accuracy of neurosurgery was greatly increased with the introduction of the stereotactic frame in 1947 which allowed neurosurgeons to plan and execute operations with millimetre precision.

51. For many years these precise neurosurgical operations used irreversible lesions which were nevertheless often successful in alleviating the symptoms of movement disorders such as tremor and even for non-movement disorders such as chronic pain. The effects on non-movement disorders may seem less obvious, but while researchers like Sherrington were less interested in the non-movement brain processes of motivation and emotion, it has become clear that they are closely connected to movement. Many experiments have now implicated brain structures in places such as the *basal ganglia* and the *thalamus* in both movement and non-movement disorders.

52. Some of the early neurosurgical pioneers such as Bob Heath and J Lawrence Pool therefore started stimulating brain structures therapeutically in the 1950s and had some success with intermittent electrical stimulation for the treatment of, for example, chronic pain.

53. The first long-term stimulation for movement disorders took place in the former USSR in the late 1960s and was performed by the formidable Natalia Bechtereva who did not have access to implantable stimulators and instead intermittently stimulated implanted electrodes in outpatients. By the 1980s manufacturers were able to supply batteries sufficiently small for neurosurgeons to implant them for use with the deep brain electrodes.





Deep brain stimulation for chronic pain

At the top is shown a three-dimensional rendering of the human brain with the placement of the two electrodes in the PVG/PAG and thalamus in relation to some of the important subcortical structures such as the brain stem and cerebellum. At the bottom is shown the connectivity of the PVG/PAG which is widespread as measured with diffusion tensor imaging in the living human brain.

Animal models for Parkinson's disease

54. The real tipping point for deep brain stimulation took place after a series of animal experiments by two competing teams, led by Tipu Aziz and Hagai Bergman, in the late 1980s. Both teams had been experimenting on parkinsonian monkeys to find a potential cure and were independently able to show that lesions of the subthalamic nucleus could help with some of the symptoms.

55. This finding was made possible by the accidental discovery by a group of very unfortunate drug users who thought they were injecting a synthetic opioid drug (MPPP) but instead injected the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) which rendered them parkinsonian. The neurotoxin selectively destroys dopaminergic neurones in a part of the basal ganglia called the substantia nigra and this in turn creates symptoms like those seen in patients with Parkinson's disease.

56. The accident paved the way for an experimental model of Parkinson's disease in monkeys. Following the discovery of the importance of the subthalamic nucleus in Parkinson's disease, Abdelhamid Benazzouz showed in 1993 that stimulation of this brain structure can lead to reversal of many of the crippling symptoms in monkeys and soon afterwards this was also demonstrated in humans. The discovery of the importance of the subthalamic nucleus has been highly influential and at least 30,000 patients worldwide have since been helped by deep brain stimulation of this brain region.

57. Sadly, this treatment does not work for all patients. This led to a search for alternative treatments. The research started in the early 1990s with his initial discovery – with the initial discovery, by Alan Crossman of the University of Manchester, of a change in the neural activity in the pedunculopontine nucleus in the brainstem of a monkey that had MPTP injected in only one side of the brain and therefore only showed parkinsonian symptoms on one side of the body.

58. Careful experiments with full characterisation of the activity in this brain region of monkeys followed over the following decade. It became clear from animal research that some human patients such as Julia were likely to benefit from deep brain stimulation. This was finally confirmed in 2004 by two research teams in Bristol, UK, and Rome, Italy, led by Steven Gill and Paulo Mazzone. Since then many groups around the world have successfully used this technique in human patients.

Principles of stimulation

59. Despite the remarkable success of deep brain stimulation for many different treatment-resistant disorders, the underlying neural mechanisms are still not well understood. In particular, it is not well understood how the stimulation in deep regions of the brain drives activity in wider brain areas such as the cortex and subcortical regions.

60. Initially, many researchers thought that deep brain stimulation worked in similar ways to lesions, since they often have the same clinical outcome. But this is unlikely, given that different stimulation parameters in the same brain region can lead to very different results. Stimulation at low frequency in the thalamus can, for example, decrease and alleviate chronic pain, while in contrast high frequency stimulation can lead to a sharp increase in pain.

61. The brain functions through different brain regions communicating via multiple oscillatory loops of activity, and some of this activity may become altered by disease states, sometimes with malignant consequences. Currently, the weight of the scientific evidence suggests that the most likely mode of action for deep brain stimulation is through stimulation-induced modulation of this oscillatory brain activity in widespread brain areas.

Brain imaging

62. It has, however, been difficult to measure the effects of deep brain stimulation in the rest of the brain. Brain imaging techniques such as positron emission tomography and functional magnetic resonance imaging (fMRI) are too slow to capture the transient neural activity on the scale of milliseconds. In fact, the strong magnetic fields of magnetic resonance imaging have been shown to be very dangerous to use with deep brain stimulation. Instead, other neuroimaging techniques must be used to study the whole brain changes induced by deep brain stimulation and for this purpose magnetoencephalography is used. This brain imaging method is able to track neural changes directly over milliseconds and with a spatial precision of millimetres.

Current human indications for deep brain stimulation

Disorder	Established site	Promising site	Potential site
Parkinson's disease	• Motor thalamus • Globus pallidus internal segment • Subthalamic nucleus • Pedunculopontine nucleus (in brainstem)		
Dystonia	Globus pallidus internal segment		
Essential tremor	Motor thalamus		
Pain	Sensory thalamus, periventricular grey, periaqueductal grey		
Cluster headache	Posterior hypothalamus		
Depression		Subgenual cingulate, nucleus accumbens	Orbitofrontal cortex, anterior cingulated cortex, ventral pallidum, medial dorsal thalamus
Obsessive compulsive disorder	Anterior limb of internal capsule		

63. Robert, whose leg was amputated following a fall and who developed excruciating chronic pain in his phantom leg, had his brain scanned in this way. His chronic pain was alleviated by deep stimulation of the periaqueductal grey in the upper brainstem, but it was interesting to discover which other brain regions were involved in this change in his subjective state. When the stimulator was turned off, Robert reported significant increases in his subjective pain. When the stimulator was turned on, this led to pleasurable pain relief. When this happened, corresponding significant changes in brain activity were found in a network that comprised the regions of the emotional brain and included the mid-anterior orbitofrontal cortex (just over the eyeballs).

64. This corresponds well to previous research by Predrag Petrovic from the Karolinska Institute which has used brain imaging to show that this region is essential to the alleviation of pain in placebo responders. In many other brain imaging experiments, it has also been shown that the orbitofrontal cortex is important for hedonic experience in general.

Potential complications and side effects

65. While DBS is helpful for some patients, there is also the potential for neuropsychiatric side effects. Reports in the literature describe the possibility of apathy, hallucinations, compulsive gambling, hypersexuality, cognitive dysfunction, and depression. However, these may be temporary and related to correct placement and calibration of the stimulator and so are potentially reversible. A recent trial of 99 Parkinson's patients who had undergone DBS suggested a decline in executive functions relative to patients who had not undergone DBS, accompanied by problems with word generation, attention and learning. About 9% of patients had psychiatric events, which ranged in severity from a relapse in voyeurism to a suicide attempt. Most patients in this trial reported an improvement in their quality of life following DBS, and there was an improvement in their physical functioning.

66. Because the brain can shift slightly during surgery, there is the possibility that the electrodes can become displaced or dislodged. This may cause more profound complications such as personality changes, but electrode misplacement is relatively easy to identify using CT. There may also be complications of surgery, such as bleeding within the brain.

67. After surgery, swelling of the brain tissue, mild disorientation and sleepiness are normal. After 2–4 weeks, there is a follow-up to remove sutures, turn on the neurostimulator and program it.

68. The major risks of the DBS procedure include paralysis, coma and/or death, bleeding inside the brain (intracranial haemorrhage), leakage of fluid surrounding the brain, and seizures.

69. Side effects of brain stimulation include tingling sensation, and temporary worsening of the patient's disease symptoms, speech problems like whispering and trouble forming words and vision problems.

70. One case series reported that the pulse generator failed in 50% (6/12) of patients. Across three case series where it was reported as an outcome, displacement of the stimulating electrode occurred in 6% (1/18), 8% (1/12) and 15% (8/52) of patients. The incidence of lead fracture or failure in three studies was 4% (2/52), 5% (1/22) and 6% (1/18). These complications sometimes required further surgery.

71. One case series of 22 patients who underwent deep brain stimulation for dystonia reported transient oedema of the frontal lobe, cutaneous necrosis of the scalp, localised skin infection and haematoma near the neurostimulator, in one patient each. However, none of these events had permanent sequelae.

72. It was noted that adverse events relating to this procedure include infection, haemorrhage (possibly causing hemiparesis), hardware failure, dysarthia, speech disturbance, cerebral oedema and death. They also noted that theoretical complications include stroke, speech impairment, cognitive impairment, depression, suicide and risk of injury during subsequent magnetic resonance imaging.

The future

73. Deep brain stimulation combined with a non-invasive brain imaging technique such as magnetoencephalography thus offers a unique window on the general mechanisms of brain function. From a systems neuroscience point of view, deep brain stimulation is rather exciting since its causal, interventional nature offers unique opportunities to understand the brain and the mind. It is, however, imperative that we proceed with a combination of humility and hubris. While tinkering with the very core of what makes us human, the lessons from psychosurgery of the last century must not be forgotten and clear ethical guidelines must guide future experiments.

Facts: deep brain stimulation

- Deep brain stimulation in select brain regions has become the basis of highly successful therapies for treating otherwise treatment-resistant disorders.
- Careful animal experimentation has demonstrated that deep brain stimulation is both safe and efficacious, and has helped establish all of the current deep brain targets.
- The weight of the evidence so far suggests that the most likely mode of action for deep brain stimulation is through stimulation-induced modulation of oscillatory brain activity.
- Deep brain stimulation is both an important tool for clinical use and for obtaining novel insights into the nature of the mind.

74. With these caveats in mind, the future of deep brain stimulation is wide open with the current technology comparable to that of the early cardiac pacemakers. Although some stimulation parameters can be altered after surgery, it essentially relies on open-loop continuous stimulation with little dynamic possibility for adjustment to the individual and the risk of stimulation-induced side-effects. However, the possibility of recording signals from the electrode opens up the prospect of developing sophisticated closed-loop, demand-driven pacemakers. More generally, it is already now possible to make advanced brain-computer interfaces using deep brain stimulation.

75. But even more importantly, deep brain stimulation has the potential to transform our understanding of the mind. As we saw with the patients with cluster headache and chronic pain, direct stimulation of the brain can change our subjective experience of pleasure and this knowledge may for instance come to help us to a better understanding of depression and in particular the lack of pleasure, *anhedonia,* which is one of its key features.

76. Already, several groups around the world are trying to use deep brain stimulation to alleviate depression. The question remains, however, whether we should expect the magic of deep brain stimulation to work on something as complex. Research has shown how one of the most important determinants of pleasure, and perhaps even happiness, lies in the complex patterns of social interactions.

77. Perhaps it is ultimately too much to ask of deep brain stimulation to be able to help with such higher functions of the social mind. Meanwhile, however, deep brain stimulation remains an important clinical tool to restore normal functioning – and with great potential to reveal some of the secrets of the brain and mind.

Acknowledgements
National Institute for Health and Clinical Excellence (2006) Adapted from *IPG 188 Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease)*. London: NICE. Available from HYPERLINK "http://www.nice.org.uk/guidance/IP188"www.nice.org.uk/guidance/IP188 Reproduced with permission.

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