

# Deep brain stimulation

Researchers can electrically stimulate the brain to help with treatment-resistant disorders such as Parkinson's disease and chronic pain – and this is now starting to yield new insights into the mind.

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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 aging population in the developed world this imposes a heavy burden on society. Many parkinsonian patients can be helped for some years by drugs such as *levodopa* or dopamine agonists. But unfortunately approximately one tenth of them do not respond to this drug.

Julia finds it very difficult to initiate movement and to keep her balance. 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*.

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.

## Chronic 'suicide headaches'

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 limb pain or cluster headache.

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 a deep depression and almost to suicide.

The precise anatomical information acquired from brain imaging combined with the use of a stereotactic frame allows the neurosurgeon to implant electrodes into 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 as our team implanted an electrode with four contacts in the hypothalamus in the centre of his brain. This target is based on functional brain imaging experiments of patients suffering from cluster headache which have shown that the focus of the disease lies in the posterior hypothalamus.

As it happened, Jamie had an attack of cluster headache on the operating table which we were able to record with the deep brain electrodes. But this was the last cluster headache Jamie has had, and the deep brain stimulation has subsequently transformed his life.

We connected the battery and some days later, once we had ascertained that his cluster headaches had truly stopped, a long-lasting battery was implanted subcutaneously over Jamie's right breast

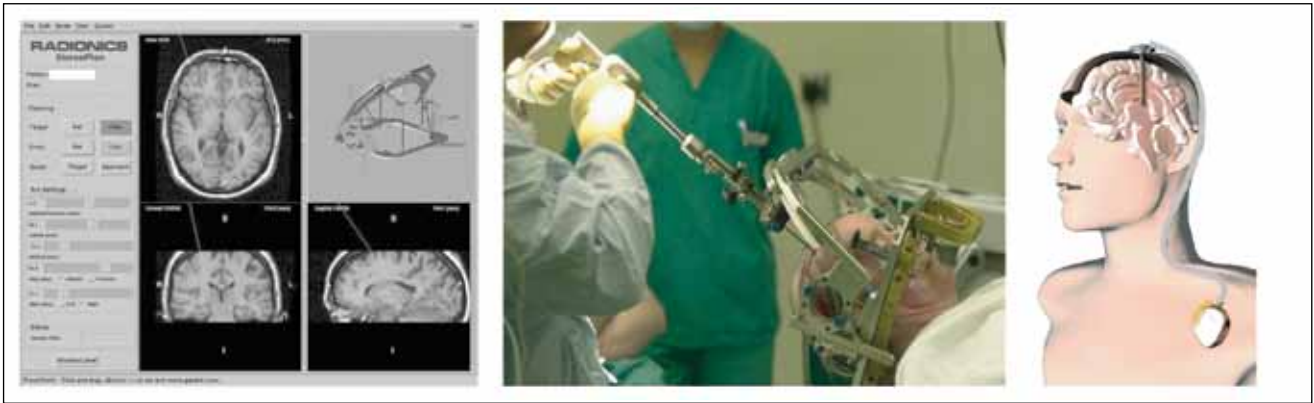


Figure 1. The neurosurgical procedures involved in DBS. The patient is scanned with a stereotactic frame and the neurosurgery is preplanned using stereotactic planning software (left). The precise positioning of the electrode is performed through perforating the calvarium with a twist drill (middle). The electrode is secured to the skull using a titanium miniplate and the implantable pulse generator is placed in a subcutaneous pectoral pouch. Here is shown the relative positions of the electrode, lead and battery within a patient's head and chest (right).

muscle and connected permanently to the deep brain electrodes. Through a remote control, we can change the frequency, pulse width, and voltage of the stimulation to obtain the best possible parameters for alleviating his cluster headache should it come back. If need be, we can even remove the electrodes completely.

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.

### A brief history of neuromodulation

So how does the magic of deep brain stimulation work? However magical it may look, the alleviation of Julia's and Jamie's symptoms is obviously not the product of magic but of careful scientific experimentation (Kringelbach *et al.*, 2007b).

It has been known for some time that electricity plays an important role in the body (Gildenberg, 2005). 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.

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".

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 an-

imal 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.

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.

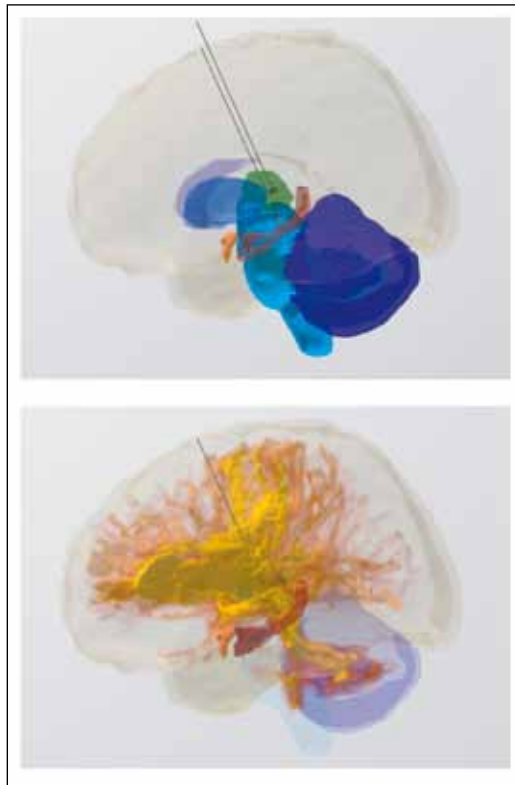
The effects on non-movement disorders may seem less obvious but while researchers like Sherrington were less interested in the non-movement brain processes of motivation and emotion, it has become clear that they are closely connected to movement. Many experiments have now implicated brain structures in places such as the *basal ganglia* and the *thalamus* in both movement and non-movement disorders.

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.

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.

**Figure 2.** Deep brain stimulation for chronic pain. At the top is shown a three-dimensional rendering of 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 brainstem (light blue) and cerebellum (dark blue). 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

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 (Aziz *et al*, 1991; Bergman *et al*, 1990).

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 neurons 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.

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 (Benazzouz *et al*, 1993).

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.

Sadly, this treatment does not work for all patients which led one of us (Tipu Aziz) to search for alternative treatments. The research started in the early 1990s with his initial discovery – with Alan Crossman of 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.

Careful experiments with full characterisation of the activity in this brain region of monkeys followed over the following decade. It became clear from our animal research that some human patients such as Julia were likely to benefit from deep brain stimulation (Nandi *et al*, 2002). 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

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.

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 (Owen *et al*, 2006). This shows how pain and pleasure are clearly related to each other in the brain, but also how we need more sophisticated models to describe how deep brain stimulation work.

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 scien-

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 gray periaqueductal gray	Anterior cingulate cortex	Orbitofrontal cortex
Cluster headache	Posterior hypothalamus		
Depression		Subgenual cingulate, nucleus accumbens	Orbitofrontal cortex, anterior cingulate cortex, ventral pallidum, medial dorsal thalamus
Obsessive-compulsive disorder	Anterior limb of the internal capsule		

tific 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 (Brown *et al.*, 2004).

### Brain imaging

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 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 we were recently able to use magnetoencephalography (Kringelbach *et al.*, 2007a). This brain imaging method is able to track neural changes directly over milliseconds and with a spatial precision of millimetres.

We scanned a patient, Robert, whose leg was amputated following a fall and who developed excruciating chronic pain in his phantom leg. We had successfully alleviated this chronic pain by deep stimulation of the periaqueductal gray in the upper brainstem but were interested 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 we found corresponding significant changes in brain activity in a network that comprised the regions of the emotional brain and includes

the mid-anterior orbitofrontal cortex (just over the eyeballs).

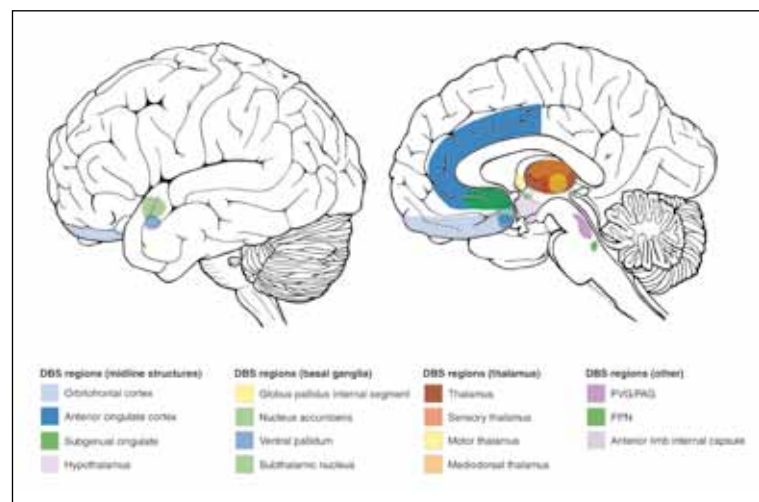
This corresponds well to previous research by Predrag Petrovic from the Karolinska Institute which has used brain imaging to show that this region is essential to the alleviation of pain in placebo responders. We have also shown in many other brain imaging experiments that the orbitofrontal cortex is important for hedonic experience in general (Kringelbach, 2005).

### The future

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 pro-

**Figure 3.** Existing and possible future brain targets for DBS. The figure shows the approximate placement of some of the established, promising and potential sites for DBS which is further elaborated in the table.



**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.

ceed 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 (Kringelbach and Aziz, 2009).

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.

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.

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.

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.

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**Online material: videos of DBS patients on and off stimulation**

Some patient videos can be found at: [www.kringelbach.dk/nrm](http://www.kringelbach.dk/nrm)

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