Translational principles of deep brain stimulation

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Abstract | Deep brain stimulation (DBS) has shown remarkable therapeutic benefits for patients with otherwise treatment-resistant movement and affective disorders. This technique is not only clinically useful, but it can also provide new insights into fundamental brain functions through direct manipulation of both local and distributed brain networks in many different species. In particular, DBS can be used in conjunction with non-invasive neuroimaging methods such as magnetoencephalography to map the fundamental mechanisms of normal and abnormal oscillatory synchronization that underlie human brain function. The precise mechanisms of action for DBS remain uncertain, but here we give an up-to-date overview of the principles of DBS, its neural mechanisms and its potential future applications.

Dystonia
A movement disorder that leads to involuntary sustained muscle contractions, causing distorted posturing of the foot, leg or arm.

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The modulation of brain activity by way of direct electrical stimulation of the brain has been in use since 1870, when it was shown that electrical stimulation of the motor cortex in dogs can elicit limb movement[1]. Electrical stimulation was introduced as a tool for improving neurosurgical procedures in humans from as early as 1884 (REF. 2). In modern times, the implantation of deep brain stimulation (DBS) pacemakers in specific brain regions has become the basis of highly successful therapies that alleviate the symptoms of otherwise treatment-resistant disorders such as chronic pain[3,4], Parkinson's disease[5,6], tremor[7,8] and dystonia[9] (BOXES 1,2; Supplementary information S1–S4 (movies)). Despite its long history of use, however, it is still unclear how DBS works. Nevertheless, translational research has helped to elucidate not only the neural mechanisms and targets that underlie the effects of DBS (TIMELINE), but also the fundamental brain functions that are affected in the disorders for which DBS is used.

Here, we review the evidence from neurophysiological recordings in animals and humans, as well as data concerning neurotransmitter release, and findings from functional neuroimaging studies that are relevant to DBS. This is synthesized into a model of the neural and systems-level mechanisms of DBS. We then discuss examples of how brain targets for DBS have been developed using translational research, focusing on the subthalamic nucleus (STN) and the brainstem pedunculopontine nucleus (PPN) to demonstrate how lesion studies, DBS and electrophysiological recordings in animals have been translated into the development of clinical interventions in humans. Finally, we explore some of the future possibilities for refining and expanding the use of DBS. This is a particularly exciting time for DBS, as the demonstration of the long-term efficacy of DBS as a treatment for movement disorders such as Parkinson's disease, tremor and dystonia, as well as for chronic pain, has now opened the possibility to develop novel targets in affective and other non-movement disorders, such as depression and bipolar disorder.

Overall, from a systems neuroscience point of view, the causal and interventional nature of DBS is especially exciting. This potential can be harnessed by combining DBS with non-invasive neuroimaging methods, offering the possibility of mapping the spatiotemporal unfolding of DBS-elicited whole-brain activity, including the normal and abnormal oscillatory synchronizations. DBS directly changes brain activity in a controlled manner, and its effects are reversible, unlike those of lesioning techniques. DBS is also the only neurosurgical method that allows blinded studies. Mapping the effects of this causal intervention is likely to help us unravel the fundamental mechanisms of human brain function.

Neurophysiological principles of DBS

Traditionally, the point of departure for understanding the mechanisms of DBS has been to compare the effects of stimulating a particular brain area with the therapeutic outcomes of neurosurgical lesions. This presents the general question of whether DBS inhibits or excites neurons. We address this deceptively simple question in the section on models of DBS mechanisms.

Neural elements
The cell body, myelinated axons, dendrites and supporting glial cells.

Bradykinesia
The slowing of, and difficulty in initiating, movement that is characteristic of Parkinson's disease.

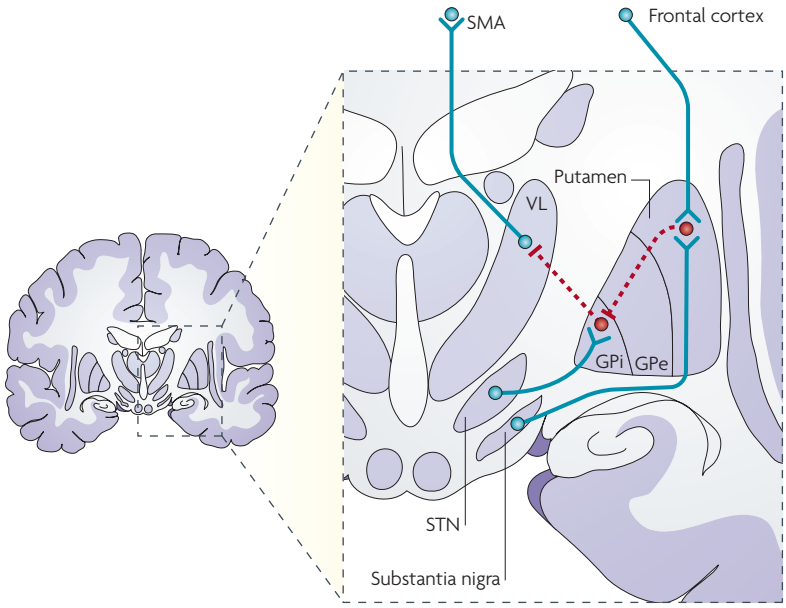
DBS of both the normal and the diseased brain fundamentally depends on a number of parameters, including the physiological properties of the brain tissue, which may change with disease state, the stimulation parameters (including amplitude and temporal characteristics), and the geometric configuration of the electrode and the surrounding tissue.

Physiological properties. The physiological — specifically, the electrical — properties of normal and diseased brain tissue depend on the presence of different types of neurons and supporting glial cells, which use different types of ion channels with variable voltage-sensitive properties. Myelinated axons are the most excitable neural elements[10,11]. The effect of DBS on the various neural elements depends on the nonlinear relationship between the stimulus duration (pulse width) and the amplitude (voltage or current) that is necessary to stimulate the neural element[10]. The minimal current necessary to stimulate a neural element with a long stimulus duration is called the rheobase (the amplitude threshold). The chronaxie time is the minimum length of time that is required to excite a neural element using half the intensity that elicits a threshold response. The chronaxie of myelinated axons is around 30–200 μs, whereas the chronaxies of cell bodies and dendrites are substantially larger, at around 1–10 ms. This means that with normal DBS parameters, the postsynaptic responses result from the activity of efferent axons rather than of cell bodies[12,13] (FIG. 1a,1b).

Stimulation parameters. The general therapeutic stimulation parameters of DBS have been derived, primarily by trial and error, from the almost immediate effects on, for example, tremor, rigidity, bradykinesia, paresthesia and chronic pain in patients during surgery[14]. The exact DBS parameters, including the stimulus amplitude, duration and frequency band, vary with the treatment and with the targeted brain region. At present, with most commercially available stimulators, these parameters can be externally changed and fine-tuned over time. However, the technology allows only open-loop continuous stimulation, which is not adaptive and does not take into account the continuous neural feedback from the individual patient. Instead, only the patient's current behavioural state is used as an indicator of how to change the parameters externally. This is not always efficient, and the technique can give rise to stimulation-induced side-effects. In some ways the status of the technology is like that of cardiac pacing technologies 20 years ago, and the field is wide open for further innovation.

Geometric configuration. The geometric configuration of the neural elements in relation to the electrode influences the effects of the stimulation on local and distal neural elements. For example, the orientations of local neural elements such as the axons and the cell body are important determinants of neural responsiveness[10]. Furthermore, the effects on distal neural elements depend on the distance between the neural elements and the electrode: both the rheobase and the chronaxie rise in proportion to the distance, which means that the responsiveness of more distal elements decreases as the distance from the electrode increases[12]. Thus, the stimulation volume is not a fixed cylinder around the stimulation electrode, but rather it varies with the position of the electrode and the properties of the surrounding neural tissue. The parameters that are normally used in clinical settings lead to the stimulation of a large volume of neural tissue[11]. For example, modelling of the excitability effects for STN stimulation using realistic white-matter pathways has shown that the stimulation is probably not limited to the STN proper, which is consistent with known DBS side-effects[11]. Finally, currents greater than eight times the threshold from monopolar cathodes can block action potentials in axons. This leads to the intriguing hypothesis that

Box 1 | **Deep brain stimulation (DBS) in movement disorders**



DBS for the treatment of movement disorders such as Parkinson's disease, dystonia and tremor has mainly targeted structures in the basal ganglia. The translational 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model for Parkinson's disease has highlighted the internal globus pallidus (GPi) and the subthalamic nucleus (STN) as safe and efficacious targets[66,67] (see figure). The long-term effects of using high-frequency (130–185 Hz) DBS for Parkinson's disease are well documented[5,6]. DBS trials for Parkinson's disease have shown substantial improvements in symptoms, as measured by motor and daily living scores,[99] as well as reductions in the patients' medication[6,100,101]. Recently, translational research has identified the pedunculopontine nucleus as a potential new Parkinson's disease target in monkeys[80,81,102,103] and humans[82–84].

The preferred target for dystonia and spasmodic torticollis is the GPi[104,105]. The most commonly used DBS parameters for dystonia differ from those for Parkinson's disease, with a broader pulse width (200–400 μs) and higher voltage (typically between 2.2 and 7 V), leading to rapid battery consumption[106]. Blinded, controlled GPi trials have shown 30–50% improvements in patients over 12 months[9].

Essential tremor is usually treated with DBS in the ventral intermediate nucleus of the thalamus (Vim)[107,108], whereas the DBS target for Parkinson's disease tremor is the STN[109]. Long-term effects of DBS in Vim have produced an average tremor reduction of over 80% in most patients[7,8]. Thalamic DBS was found to significantly improve tremor, as compared with thalamotomy, and to have fewer adverse effects[110]. A large multicentre study showed continued improvements in tremor ratings in essential tremor patients after 6 years of follow-up[111]. In the figure, blue lines represent stimulatory connections, red dotted lines represent inhibitory connections. GPe, external globus pallidus; SMA, supplementary motor area; VL, ventrolateral nucleus of the thalamus.

Frequency band
Neural oscillations have been classified into different frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz), gamma (30–80 Hz), fast (80–200 Hz) and ultra fast (200–600 Hz).

Open-loop stimulator
An open-loop stimulator is a simple type of non-feedback controller whereby the input into the brain region is determined using only the current behavioural state and a model of the system.

6-hydroxydopamine
(6-OHDA). The first agent used to model Parkinson's disease. Injection of 6-OHDA into the substantia nigra causes it to selectively accumulate in dopamine neurons, and then kill them as a result of toxicity that is thought to involve the generation of free radicals. 6-OHDA can produce non-specific damage to other neurons.

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
(MPTP). A neurotoxin that causes degeneration of dopaminergic neurons in the substantia nigra and hence is used to study the pathophysiology of Parkinson's disease.

Box 2 | **Deep brain stimulation (DBS) in affective and other non-movement disorders**

DBS for the treatment of affective and related disorders, including depression, obsessive-compulsive disorder, Tourette's syndrome, chronic pain and cluster headache, has so far been based mostly on human research, as few, if any, reliable animal models for these disorders exist. However, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model may be useful for studying the effects of DBS in some affective disorders because many of the brain structures affected in this model are also implicated in affective disorders. This is also highlighted by the fact that severe depression can be reversibly induced with DBS for Parkinson's disease[93,112].

DBS for the treatment of chronic pain has been used for over 50 years, since the initial studies in which DBS was applied to the hypothalamus[113]. More recently discovered efficacious targets are the thalamus[114–116] and the periventricular/periaqueductal grey region (PVG/PAG)[117–120]. However, following two failed clinical trials[121], device manufacturers did not seek FDA approval for DBS in these brain regions. During the last decade only five centres outside the United States have produced case series of more than six patients who underwent DBS for the treatment of pain[3,4,122–128]. These studies showed significant improvements in patients with pain after amputation and stroke, and head pain including anaesthesia dolorosa. Patients with cluster headache have been successfully treated with DBS in the hypothalamus[129,130].

Affective disorders have also been successfully treated with DBS. Targets for the treatment of depression include the inferior thalamic peduncle[131,132] and the subgenual cingulate cortex[51]. DBS for the treatment of obsessive-compulsive disorder has targeted the anterior internal capsule[133], and DBS of the thalamus[134] and GPi[135] has been reported effective in treating Tourette's syndrome. The ethical implications of DBS for the treatment of affective disorders should be carefully considered to avoid comparisons to the psychosurgery of last century — but it should be remembered that DBS is reversible, in principle.

Stereotactic procedures always carry a significant risk, and they can lead to intracranial bleeding, as occurs with approximately 2.0–2.5% of DBS implants[101,136]. Other potential complications include hardware-related complications such as dislocation, lead fracture and infection. The infection rate is equal to that of other surgical procedures, but infection may necessitate explantation of the stimulator[137]. Stimulation-induced side effects, such as paresthesia, tonic muscle contractions, dyskinesia and gait ataxia are also reported, as are the less common aggression[138], mirthful laughter[92], depression[93], penile erection[94] and mania[139].

stimulation from an electrode blocks somatic activity in nearby elements and only causes sub-threshold activity in distal elements, leaving the myelinated axons of intermediate neural elements the most likely to receive the effects of stimulation and pass them on to mono- and poly-synaptically connected brain structures[15] (FIG. 1c).

The relative contribution of the above three parameters to the effects of DBS on local and whole-brain activity have been assessed experimentally in humans and other animals through direct neural recordings[16–20], neurochemistry[21,22] and functional neuroimaging methods[23–26]. In addition, computational modelling can be used to test and predict the effects of DBS on simulated neural elements[11].

Neurophysiological recordings during DBS

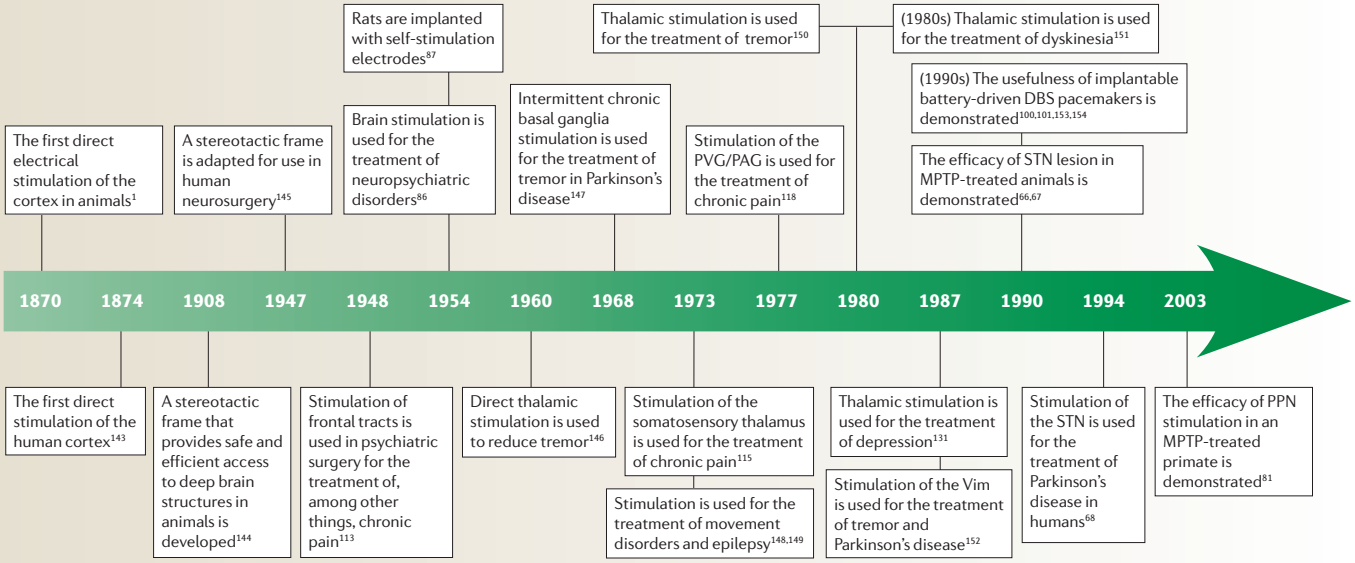
Many of the general principles of neural processing are preserved across species and, therefore, data from DBS studies for movement disorders in animals such as rats and non-human primates are highly relevant for understanding the mechanisms that underlie the effects of DBS in humans. We concentrate here on the effects of *in vivo* stimulation on neural activity in local and distal elements, and will not discuss the results of the many *in vitro* studies, which have been reviewed elsewhere[27].

Many of the direct neurophysiological *in vivo* recordings obtained thus far have used DBS in animal models of Parkinson's disease, of which the 6-hydroxydopamine (6-OHDA)-lesioned rat and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primate have been the most successful[28]. In monkeys, it is possible to stimulate the STN and the internal globus pallidus (GPi) while recording from other brain regions. In rats, one can only stimulate the STN, as stimulation of the rat homologue of the GPi — the entopeduncular nucleus in the internal capsule — gives rise to confounding effects from concomitant stimulation of fibres of passage.

In one study, high-frequency stimulation of the STN in anaesthetized normal and 6-OHDA-lesioned rats induced a net decrease in activity in all cells around the stimulation site[29]. In addition, it caused inhibition of most neurons in the substantia nigra pars reticulata (SNpr) in normal rats and of the neurons in the substantia nigra pars compacta (SNpc) in both 6-OHDA-lesioned rats and rats with lesions of the GP. Conversely, activity was increased in most neurons in the ventrolateral thalamus in the normal rats. However, the results of this study should be treated with caution, as neural activity could only be recorded during post-stimulation periods. Another study using anaesthetized normal rats showed that high-frequency STN stimulation induced a decrease in the activity of SNpr neurons at low intensity and an increase in activity at a higher intensity[30]. These results showed that transmission of cortical information through the trans-striatal pathway was preserved during high-frequency STN stimulation, whereas the effects on the trans-subthalamic pathways depended on the intensity of the STN stimulation. This finding could point to a possible method for blocking neuronal signals in particular disease states, and it is consistent with findings from studies in which the STN of cataleptic rats was stimulated with dopamine antagonists, resulting in reversed abnormal signal patterns in SNpr neurons[31].

The data from experiments in rats are consistent with findings from studies that examined the effects of STN stimulation on activity in GP neurons in MPTP-treated primates[16,32]. Neurons showed multiphasic responses of short-latency duration with alternating periods of

Timeline | **History of deep brain stimulation (DBS)**



MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PPN, pedunculopontine nucleus; PVG/PAG, periventricular/periaquaductal grey; STN, subthalamic nucleus; Vim, ventral intermediate nucleus of the thalamus.

inhibition and excitation following both low- (2 Hz) and high-frequency (136 Hz) STN stimulation[16], but only the high-frequency stimulation parameters effectively alleviated the behavioural signs of Parkinson's disease. The responses persisted for up to five minutes of stimulation and caused a significant increase in stimulus-synchronized firing patterns in most neurons. This indicates that high-frequency STN stimulation causes activation in STN efferent fibres, whereas the multiphasic response patterns point towards mono- and polysynaptic activity in other parts of the basal ganglia.

Similar results were found in another study that used single STN stimulation, which induced short-latency excitation followed by weak inhibition in neurons of the external globus pallidus (GPe) and short-latency, very short-duration excitation followed by strong inhibition in GPi neurons[32]. By contrast, bursts of high-frequency stimulation (10 pulses at 100 Hz) induced powerful excitatory responses in GPe neurons, but predominantly inhibitory responses in GPi neurons. These findings indicate that in the GPi, more complex polysynaptic responses dominate over monosynaptic responses.

It is interesting to compare these findings with recordings of thalamic activity in response to high-frequency GPi stimulation in normal, awake monkeys[17]. The activity in responsive thalamic neurons was found to be reduced in most (77%) neurons during GPi stimulation, and increased in only 16% of neurons. Low-amplitude GPi stimulation inhibited the thalamic neurons but, unlike high-amplitude stimulation, failed to block movement. This suggests that GPi stimulation has not only local effects, but also direct effects on efferent axons: it changes baseline firing rates and disrupts normal and abnormal task-related patterns of activity in postsynaptic neurons.

Human studies of STN stimulation have primarily used local rather than distal recordings. In twelve patients with Parkinson's disease, activity in STN neurons was recorded while current pulses were applied through a second STN electrode located 600 μm away, and this experiment showed that local activity was mostly inhibited[33]. Similar local inhibitory effects were found in another intraoperative study in which low frequency, low-amplitude stimulation of the GPi was carried out through an electrode located 250–600 μm away from the recording electrode[18].

One unique study describes a dystonia patient who had previously undergone implantation of a DBS pacemaker in the GPi, which did not relieve the symptoms. The patient then received a thalamic DBS pacemaker and thus it became possible to record the activity of thalamic neurons in response to GPi stimulation. The patient was under anaesthesia while the activity of seven thalamic neurons in response to GPi stimulation was recorded[19]. Four of the thalamic neurons with high firing rates were inhibited, while the activity of three low-firing rate neurons remained unchanged, which is consistent with the previous findings in monkeys[17].

Interestingly, when local field potentials (LFPs) from the GPi and the STN were recorded in four awake patients with Parkinson's disease after neurosurgery, strong increases were found in the beta frequency band (15–30 Hz) oscillatory activity in the STN of patients who were not on dopaminergic medication. This specific oscillatory activity decreased when patients started taking medication, but led instead to spontaneous synchronization at frequencies in the gamma band[34]. A subsequent study showed that therapeutically effective STN stimulation of greater than 70 Hz suppresses activity in the GP in the

Local field potential
(LFP). The extracellular voltage fluctuations that reflect the sum of events in the dendrites of a local neuronal population.

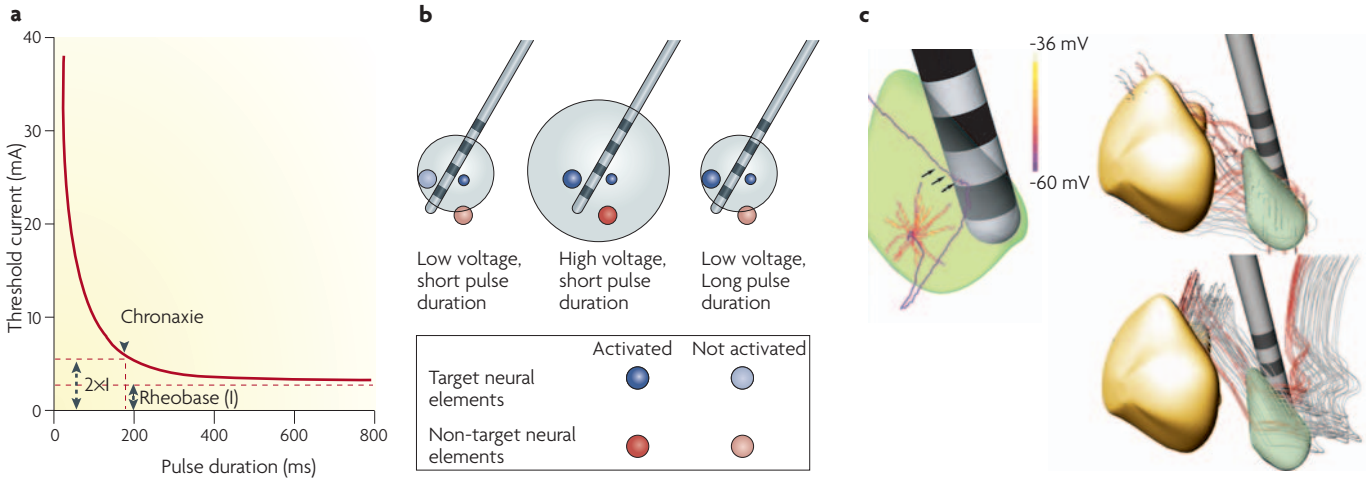


Figure 1 | **Electrophysiological principles of deep brain stimulation (DBS). a** | There is a non-linear relationship between the pulse duration and the threshold current that are necessary to stimulate a neural element. The rheobase current (I) is the minimum current that is required to stimulate the neural element with a long pulse width; the chronaxie is the pulse duration that is needed to evoke twice the rheobase current, and it can be determined from the strength–duration curve. Typical values for the chronaxie are approximately 30–200 μs for myelinated axons, and approximately 1–10 ms for cell bodies and dendrites. This means that the myelinated axons are the most likely neural elements to be affected by DBS[10,140]. **b** | The practical effects of the relationship between voltage and pulse duration on neural elements. The voltage is applied by a DBS electrode that typically has four leads (grey bars). DBS with low voltage (left) activates only some of the target neural elements (dark blue), whereas most target (light blue) and all non-target neural elements (light red) are not activated. Increasing the voltage (middle) will activate both target and non-target elements (dark blue and dark red), whereas increasing the pulse duration (right) will activate target but not non-target elements. **c** | A field-neuron model of the effects of DBS in the STN (green). The electrode is positioned in the posterior STN. The internal globus pallidus (GPi) is shown in yellow. The left panel shows how the extracellular potentials generated by the electrode create transmembrane polarization along an STN projection neuron. The neural compartments are coloured according to their transmembrane potential at the onset of a sub-threshold stimulus pulse (the neural processes have been thickened for clarity). The arrows indicate the depolarized nodes of Ranvier. The two rightmost panels show the neural activation (red) that occurs during clinically effective DBS in STN axons (top) and GPi fibres (bottom). The axons that did not respond to over 80% of the stimulus pulses are coloured grey. The panels show how the output of STN stimulation can result in the spread of the activation to STN axons and GPi fibres, which in turn can generate specific changes in the oscillatory neural activity between the cortex and the basal ganglia[141]. Part **c** modified, with permission, from REF. 141 © (2007) Elsevier Science.

beta frequency band at around 20 Hz[20] (FIG. 2a–c). This suggests that Parkinson's disease might be linked to an abnormal and potentially deleterious synchronization of basal ganglia output in the beta frequency band of around 20 Hz. Further evidence of the origin of these oscillations was recently obtained in a study of intraoperative LFP and neuronal spike recordings in the STN of fourteen patients with Parkinson's disease, which showed that the LFP beta oscillatory activity is generated mostly through spiking activity within the dorsal portion of the STN[35]. This suggests that DBS is helping to modulate the oscillatory activity which occurs between the cortex and the basal ganglia during movement (FIG. 2d).

Neurotransmitter release elicited by DBS

A number of studies have assessed the release of neurotransmitters induced by DBS in brain areas that are relevant for movement disorders. Initial studies in normal rats showed that STN stimulation increases extracellular glutamate levels in the STN, GPi and SNpr[36]. In anaesthetized 6-OHDA-lesioned rats, STN stimulation caused an increase in GABA (γ-aminobutyric acid) in the SNpr, but this increase was reversed by ibutenic acid lesions of the rat homologue of the GP[37]. Another study showed that STN stimulation at an intensity that corresponded to the threshold for inducing contralateral forelimb dyskinesia increased glutamate in the SNpr of both normal and 6-OHDA-lesioned rats[22]. By contrast, STN stimulation below this threshold did not affect glutamate levels in the SNpr of either group of rats, but it increased GABA levels in the 6-OHDA-lesioned rats only. The increase in extracellular glutamate in the GPi was not found in human patients with Parkinson's disease during clinically effective STN stimulation, who instead showed an increase of cyclic GMP in the GPi[38].

These neurophysiological results indicate that STN stimulation is likely to elicit neurotransmitter release in downstream brain structures, although it should be noted that positron emission tomography (PET) measures of [^{11}C]raclopride uptake during DBS of the STN in humans failed to show increases or decreases in striatal dopamine[39]. This contrasts with an earlier rodent PET study, in which striatal dopamine release was increased by similar stimulation[40]. Further studies are needed to clarify whether the finding of DBS-induced increases in neurotransmitters in animals is the same in humans.

Positron emission tomography
(PET). A medical imaging technique that uses injected radiolabelled tracer compounds, in conjunction with mathematical reconstruction methods, to produce a three-dimensional image, or map, of functional processes in the body (such as glucose metabolism, blood flow or receptor distributions).

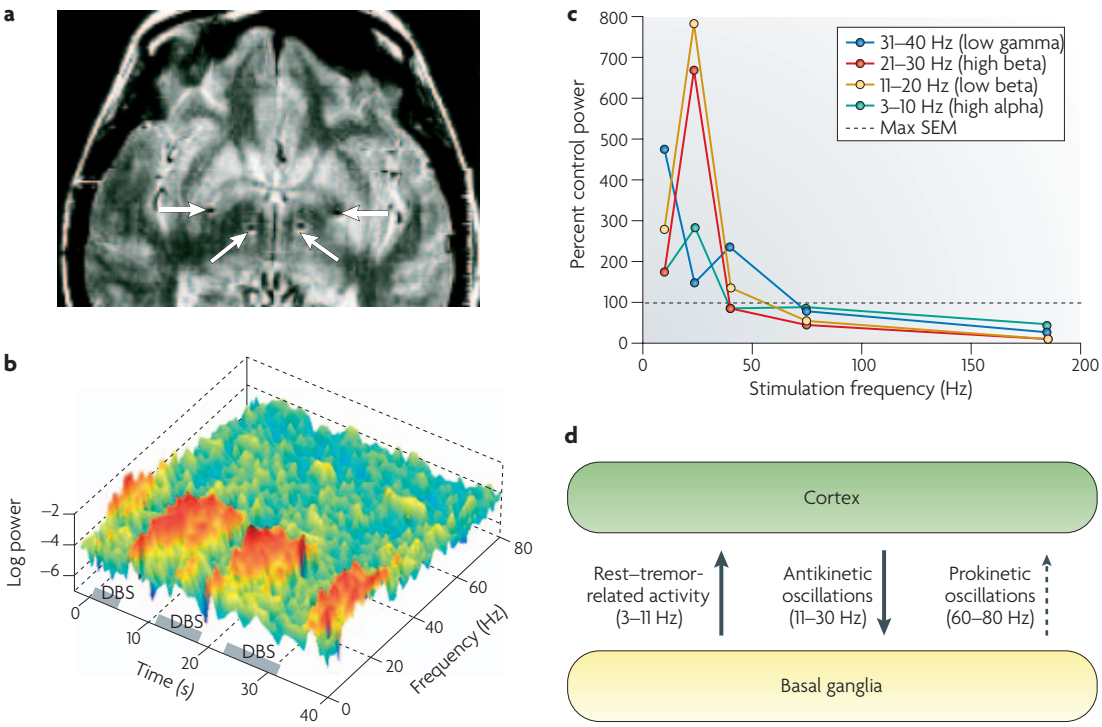


Figure 2 | **Neurophysiological recordings of deep brain stimulation (DBS). a** | A post-operative magnetic resonance image showing the placement of the DBS electrodes in the bilateral internal globus pallidus (GPi) (upper pair of arrows) and subthalamic nucleus (STN) (lower pair of arrows). **b** | A time–frequency representation of local field potentials (LFPs) recorded in the GPi during and between three periods of effective high-frequency DBS of the ipsilateral STN. DBS suppressed the prominent LFP power over 8–30 Hz. **c** | The change in LFP power represented as percent changes . LFP power fequencies below 30 Hz are maximally potentiated by low-frequency DBS (25 Hz) in the STN, whereas all activities below 40 Hz are suppressed by high-frequency DBS (greater than 75 Hz). **d** | A schematic diagram of the neural oscillations that occur in Parkinson's disease. In the absence of dopamine in the striatum, pathological oscillations arise in basal ganglia–cortical systems. These oscillations can be restored with DBS in select nuclei. Rest–tremor related activity with frequencies of 3–11 Hz arises in the basal ganglia and spreads to the cortex. The STN is driven by antikinetic oscillations in the beta band (11–30 Hz) in the cortex, whereas oscillations in the gamma band (60–80 Hz), which facilitate movement (they are prokinetic), are suppressed or absent in Parkinson's disease. SEM, standard error of the mean. Part **a** modified, with permission, from REF. 34 © (2001) Society for Neuroscience. Part **b** modified, with permission, from REF. 142 © (2007) Elsevier Science. Part **c** modified, with permission, from REF. 20 © (2004) Academic Press. Part **d** modified, with permission, from *Nature Rev. Neurosci.* REF. 58 © (2005) Macmillan Publishers Ltd.

Magnetic resonance imaging
(MRI). A non-invasive method used to obtain images of living tissue. It uses radio-frequency pulses and magnetic field gradients; the principle of nuclear magnetic resonance is used to reconstruct images of tissue characteristics (for example, proton density or water diffusion parameters).

Blood-oxygen-level-dependent signal
(BOLD signal). Local changes in the proportion of oxygenated blood in the brain, as measured by functional MRI. This proportion changes in response to neural activity, therefore the BOLD signal, or haemodynamic response, indicates the location and magnitude of neural activity.

Functional neuroimaging of DBS

Although direct neural recordings and measurements of neurotransmitter release have been useful in mapping the detailed local and monosynaptic effects of DBS, it is also important to elucidate the whole-brain responses that are elicited by DBS, and this has recently become possible with functional neuroimaging.

Neuroimaging techniques such as PET and functional magnetic resonance imaging (fMRI) can measure changes in neural activity indirectly by recording alterations in associated factors such as blood flow, blood oxygenation and glucose consumption. It is currently not entirely clear how well these indirect measurements correlate with various aspects of neural activity, but some progress has been made in our understanding of these correlations under normal physiological conditions[41,42]. In addition, it is important to realize that these methods entail a number of assumptions which may or may not prove to be important for interpreting the subsequent results.

Studies using fMRI pose a risk to DBS patients, as the strong magnetic fields involved in fMRI will interfere with active pulse generators and DBS electrodes. Moreover, although it is possible to use fMRI to scan DBS patients[43,44], there may well be significant problems associated with using the blood-oxygen-level-dependent signal (BOLD signal) as a measurement, as near-infrared spectroscopy has shown considerable variations in blood oxygenation in the frontal cortex following GPi and thalamic stimulation[45]. Extreme caution must be exercised when studying fMRI in DBS recipients, as strong heating, high induced voltage, and even sparking at defects in the connecting cable have been observed[46]. Despite these problems and risks, a single fMRI case report has been published which described STN stimulation in a patient with Parkinson's disease, and this report showed increases in the BOLD signal in primary motor areas and decreases in the BOLD signal in supplementary motor areas during stimulation[47].

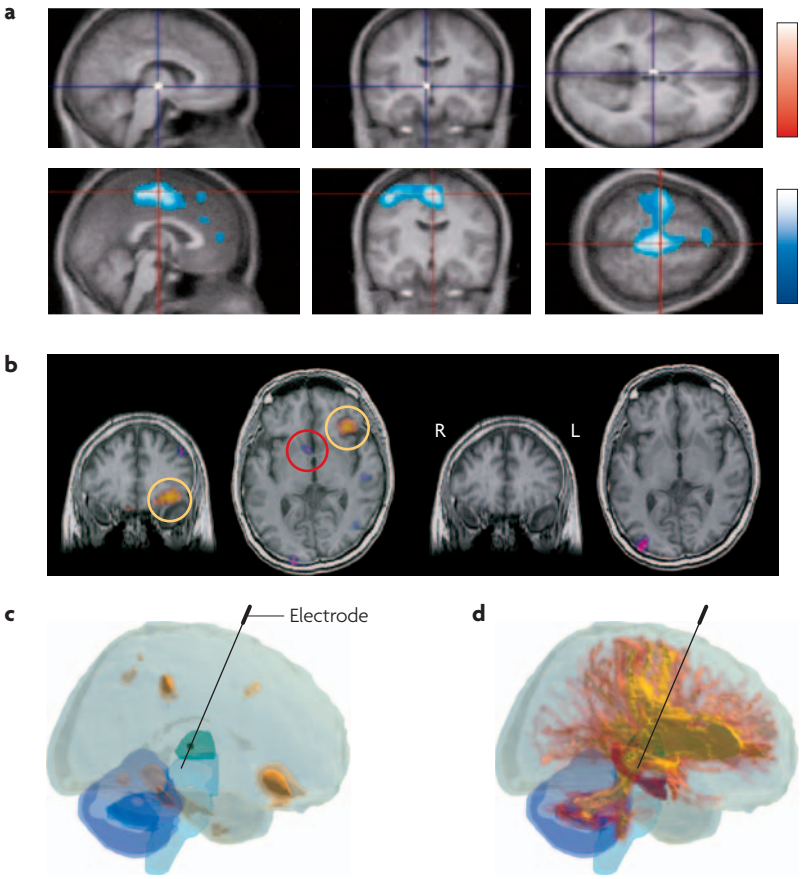


Figure 3 | **Neuroimaging scan of deep brain stimulation (DBS). a** | Significant effects of stimulation of the subthalamic nucleus (STN) on blood flow, measured with positron emission tomography (PET). Significant increases (white to red) were found in the left midbrain (top), and significant decreases (light to dark blue) were found in midline frontal to parietal cortices, bilateral somatosensory and motor areas and the prefrontal cortex (bottom)[24]. **b** | Data from a magnetoencephalography (MEG) experiment of DBS stimulation in the periventricular/periaqueductal grey area (PVG/PAG) for the treatment of phantom limb pain. When subjective pain relief was achieved with DBS, there were significant activity increases in the left mid-anterior orbitofrontal cortex and the right subgenual cingulate cortex (left coronal and axial brain slices). Activity in these brain regions was not found when DBS was turned off, with the result that significantly more pain was felt by the patient (right coronal and axial brain slices)[25]. The significant changes in event-related synchronous and desynchronous power in specific frequency bands are shown on scales from light yellow to red and from purple to dark blue, respectively. **c** | A three-dimensional rendering of the activity measured with MEG on a human brain with a DBS electrode implanted in the PVG/PAG for the treatment of chronic pain. The significant increases in activity are shown in shades of orange; the other colours represent landmark brain structures: the thalamus (green), the cerebellum (blue) and the brainstem (light blue). **d** | A three-dimensional rendering of the anatomical connectivity from the four DBS electrode contact sites in the PVG/PAG, as assessed with diffusion tensor imaging (DTI), with the probabilistic tractography presented in different colours — from more significant (yellow) to less significant (dark red). Note the extensive connections with the prefrontal cortex and in particular the orbitofrontal cortex. Panel **a** modified with permission from REF. 24 © (2003) Lippincott Williams & Wilkins.

PET has also been used for measuring the effects of DBS, and it is comparably safe, although not entirely without health risks due to the ionizing radiation used. PET has long acquisition periods; using PET in patients with Parkinson's disease and other movement disorders requires careful observation of any movement during scanning, and removal of potentially confounding scans. One PET study took such precautions while scanning patients with Parkinson's disease and showed that STN stimulation led to increased blood flow in the thalamus, GP and midbrain (including the STN) and reduced blood flow in frontal parietal and temporal cortices[24] (FIG. 3). Similarly, a PET study of stimulation of the ventral intermediate nucleus of the thalamus (Vim) in patients with essential tremor showed increases in blood flow in the thalamus and in the cortical targets of thalamic output[23]. Other studies did not monitor the movement of patients during the PET scans and must therefore be interpreted with caution[48,49]. Taken together, however, these results indicate that STN stimulation increases rather than inhibits the activity of STN output neurons, which in turn leads to increased inhibition of thalamocortical projections with subsequent decreases in blood flow in cortical regions.

Using PET to study the effects of DBS for non-movement disorders (BOX 2) is less challenging in terms of potential movement artefacts. One PET study investigated the effects of hypothalamic stimulation on cluster headache in ten patients[50]. Stimulation of the hypothalamus elicited significant increases in activity in the ipsilateral hypothalamic grey (at the site of the stimulator tip), as well as in structures in the pain-processing network, including the ipsilateral thalamus, the somatosensory cortex and praecuneus, the anterior cingulate cortex, and the ipsilateral trigeminal nucleus and ganglion. Decreases in activity were found in the posterior cingulate cortex, the middle temporal gyrus and the contralateral anterior insula. These results indicate that hypothalamic stimulation for cluster headache functions mainly by modulating the pain-processing network.

In another study, DBS stimulation of the subgenual cingulate cortex in seven patients with treatment-resistant depression caused marked reductions in mood symptoms in over half the patients and also reduced activity in cortical and subcortical areas, as measured by PET[51]. These results are, however, difficult to interpret, given the small numbers of patients and the paucity of knowledge about the brain structures involved in depression, but they again suggest that DBS works by modulating an existing network of interacting brain regions.

PET and fMRI are not, however, the only neuroimaging techniques that are currently available. Magnetoencephalography (MEG) uses superconducting quantum interference devices (SQUIDs) to measure the tiny magnetic components of the electromagnetic signals elicited by neural activity[52]. Recent advances in MEG analysis approaches, such as beamforming, have made it possible to use this method to measure the effects of DBS in patients[53]. MEG is non-invasive and almost without risk to patients, and it can provide novel spatiotemporal information about the underlying whole-brain activity. The current density of MEG sensors has increased the method's sensitivity, and the spatial resolution is now comparable to that of fMRI (typically ~5 mm^3), but with much better temporal resolution (in milliseconds)[54]. It has also been shown that activity in subcortical and deeper structures, such as the brainstem, can be measured accurately with MEG[55].

Diffusion tensor imaging
(DTI). A technique based on MRI developed in the mid-1990s in which the diffusion constants of water molecules are measured along many (>six) orientations and diffusion anisotropy is characterized. It is used to visualize the location, orientation and anisotropy of the brain's white-matter tracts, and is sensitive to the directional parameters of water diffusion in the brain.

Essential tremor
The most common neurological movement disorder. Symptoms include involuntary rhythmic movements of the limbs, head or neck.

Magnetoencephalography
(MEG). A non-invasive neuroimaging technique that detects the changing magnetic fields associated with brain activity on the timescale of milliseconds.

Beamforming method
A signal processing technique that uses receptor arrays to detect signals (for example, in MEG). These techniques can be used to determine the brain sources of signals measured from SQUIDS.

Antidromic impulse
Conduction opposite the normal, orthodromic direction, whereby an action potential moves from the starting point of the depolarization towards the axons of the neuron.

Lenticular fasciculus
The output pathway of the basal ganglia that originates in the globus pallidus and terminates in the thalamus.

The first MEG study of DBS effects was carried out in a patient who received low-frequency stimulation of the periventricular grey (PVG)/periaqueductal grey (PAG) for severe phantom limb pain[25,26]. When the stimulator was turned off, the patient reported significant increases in subjective pain. Corresponding significant changes in the elicited power of neural activity were found in a widespread network that included the mid-anterior orbitofrontal and subgenual cingulate cortices; these areas are known to be involved in pain relief[56] (FIG. 3b). MEG of patients undergoing high-frequency hypothalamic stimulation for cluster headache showed a similar pattern of changes in neural activity in a widespread cortical and sub-cortical network that included the orbitofrontal cortex[57]. Owing to its non-invasive nature and high spatial and temporal resolution, MEG holds great promise for elucidating the whole-brain neural mechanisms that are affected by DBS by, for example, measuring the oscillatory communication between brain regions[58].

A model of the mechanisms that underlie DBS

The available neurophysiological evidence for the neural and systems-level mechanisms of action of DBS can be used to draw a number of general conclusions, although it should be noted that differences between species, cell types and experimental settings make it difficult to generalize the results of different studies.

The effects of DBS depend to a large extent on the parameters listed above. They vary with intrinsic physiological properties, with the stimulation parameters (including frequency, amplitude, pulse width and duration), with the geometric configuration of the surrounding neural tissue and with the specific anatomy of the targeted region. DBS affects multiple neural elements, including myelinated axons and, to a lesser degree, cell bodies. The evidence for DBS-elicited neurotransmitter release is conflicting, and it would appear that the influence of DBS on distal brain regions is complex but mostly independent of local tissue effects.

We are now in a better position to consider some of the different hypotheses that have been put forward to explain the effects of DBS. Fundamentally, DBS is likely to either inhibit or stimulate activity in the target brain structure[59]. The similarities between the therapeutic benefits of surgical lesions and of DBS have led to the proposal of two competing principles of how DBS works: by synaptic inhibition[18] or by depolarization blockade[60]. According to the first proposal, neural output is regulated indirectly by the activation of axon terminals that make synaptic connections with neurons near the stimulating electrode; the second proposal suggests that stimulation-induced alterations occur in the activation of voltage-gated currents, which block neural output near the stimulating electrode. Recordings of local somatic activity in the stimulated nucleus can be taken as evidence for both hypotheses[18,29,60]; however, they fail to explain the occurrence of independently induced activity in distal axons. Computer modelling has shown that a decoupling of somatic and axonal activity can occur during DBS, with resultant inhibition of local neural elements but concurrent high-frequency output on efferent axons[61]. This has also been found from *in vivo* recordings in experimental animals[16,17].

At first glance it is difficult to reconcile the similar therapeutic effects of lesioning and DBS with these results. One proposal is that DBS induces synaptic depression, in which there is a synaptic transmission failure of the efferent output of the stimulated neurons as a result of neurotransmitter depletion[62]. However, evidence from *in vivo* experimental studies shows that DBS induces neurotransmitter release and sustained changes in neural activity in efferent targets[16,17,21,36,37].

This has led to the hypothesis of stimulation-induced modulation of pathological network activity[15,59,63]. One theory concerning the mechanisms that underlie Parkinson's disease is that the lack of dopamine leads to pathological oscillations in the beta frequency band between structures in the basal ganglia[20,34]. Dopaminergic medication as well as lesioning and DBS of STN and GPi targets lead to similar therapeutic outcomes in the short term, whereas both lesions and high-frequency STN stimulation suppress GP activity in the beta band.

Overall, the weight of the evidence so far suggests that the most likely mode of action for DBS is through stimulation-induced modulation of brain activity, and therefore that the similar therapeutic effects of DBS and lesioning may be achieved through different mechanisms. It is likely that the modulation comes about through the local effects of the DBS electrode on the neural activity in the DBS target, which is passed on to mono- and poly-synaptic network connections. As mentioned above, such DBS-induced modulation depends on the physiological and geometric properties of the DBS target, the stimulation parameters and the connectivity of the affected region. Stimulation of different brain targets may therefore bring about therapeutic effects in different ways.

Taking STN stimulation as an example, it is likely that the therapeutic effects of DBS depend on a number of mechanisms[15] (FIG. 1c). The different neural elements in the STN are differentially activated: somatic firing is suppressed throughout the STN, whereas the myelinated axons of projection neurons will be activated within a small volume of the applied field. Within a larger volume the afferent inputs to the STN will also be activated, whereas the projection neurons in the volume formed by the difference between the small and the larger volumes will be sub-threshold and hence suppressed by the stimulation-induced trans-synaptic inputs. The overall output of STN stimulation will thus result in high-frequency glutaminergic input to the GPe and the GPi, and it is also possible that many neurons in the GPe will be antidromically activated through their input from the STN[16]. Further spreading of the activation to GPi axons and the lenticular fasciculus is also likely, and this in turn can generate specific changes in the oscillatory neural activity between the cortex and the basal ganglia (FIG. 2). Experiments have shown that high-frequency STN stimulation leads to the suppression of all activities in the GPi that are below 40 Hz, whereas frequencies below 30 Hz are maximally potentiated by STN stimulation at 25 Hz[20] (FIG. 2a).

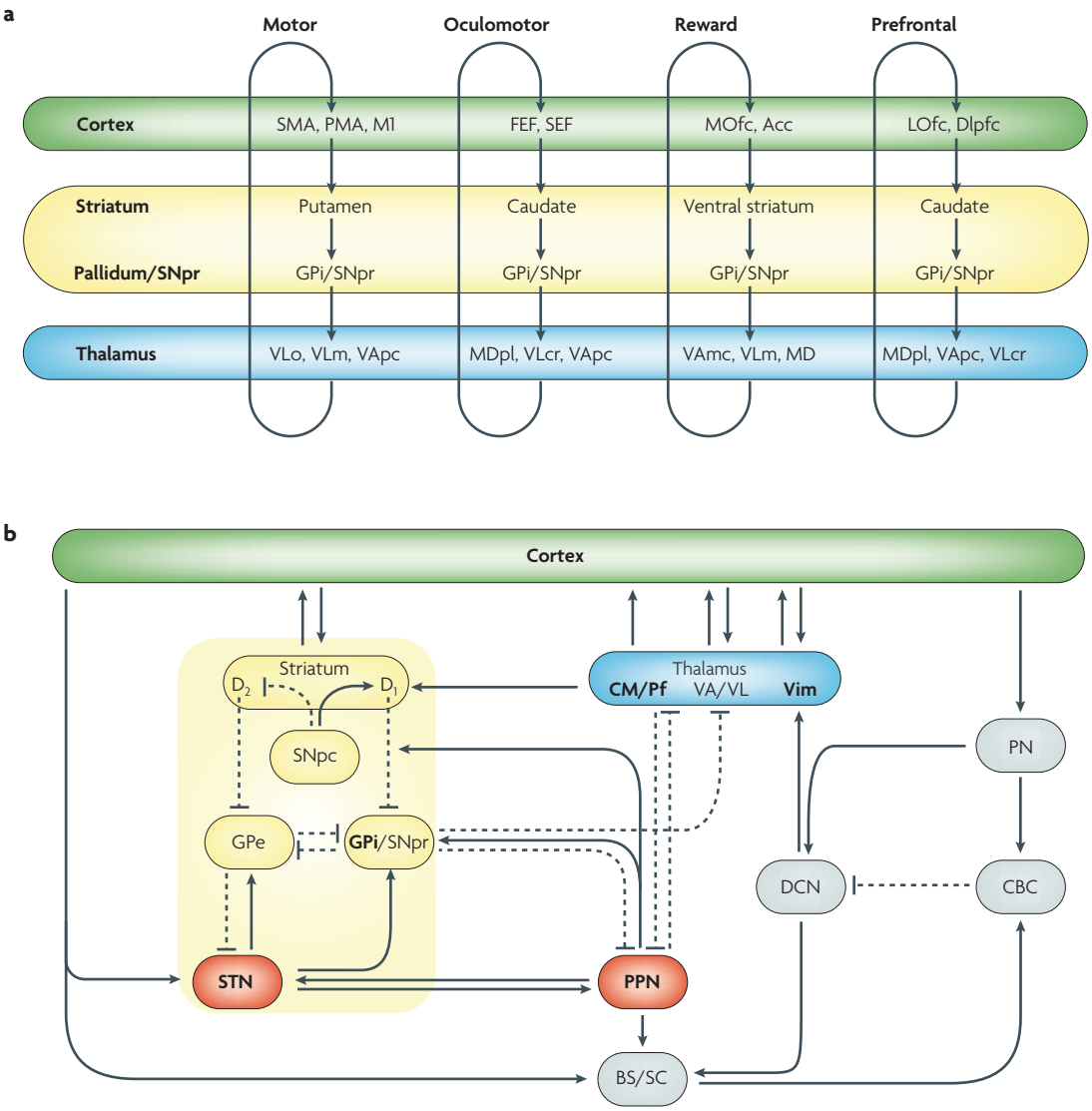


Figure 4 | **Finding new deep brain stimulation (DBS) targets for the treatment of movement and affective disorders. a** | New targets for the treatment of movement and non-movement disorders will rely on an understanding of the functions of the basal ganglia, which are implicated in many important, segregated, parallel thalamocortical circuits including the motor, oculomotor, reward and prefrontal loops. These areas have key roles in movement and affective disorders. **b** | The discovery of two new targets (red), through translational research for the treatment of the symptoms of Parkinson's disease, has been attributable to a better understanding of the detailed circuitry of the basal ganglia. According to the current understanding of basal ganglia circuitry, the input to the basal ganglia comes through the striatum, which receives most of its input from the cortex. The striatum projects through two major dopamine (D) pathways, the activity of which is controlled by the substantia nigra pars compacta (SNpc): a direct D_1 receptor-mediated pathway to the internal globus pallidus (GPi)/substantia nigra pars reticulata (SNpr), and an indirect D_2-receptor-mediated pathway involving the external globus pallidus (GPe) and the subthalamic nucleus (STN). The D_1-mediated pathway is thought to facilitate movement, whereas the D_2-mediated pathway is thought to suppress movement through activity in specific frequency bands. The GPi and SNpr send inhibitory outputs to the thalamus. DBS of select regions of the brain (in bold) have been shown to relieve some of the symptoms of Parkinson's disease. Arrows indicate excitatory (glutamatergic) pathways; dotted lines indicate inhibitory (GABAergic) pathways. Acc, anterior cingulate cortex; BS/SC, brain stem/spinal cord; CBC, cerebellar cortex; CM, centromedian nucleus of the thalamus; DCN, deep cerebellar nuclei; Dlpfc, dorsolateral prefrontal cortex; FEF, frontal eye fields; LOfc, lateral orbitofrontal cortex; GABA, γ-aminobutyric acid; M1, primary motor cortex; MD, mediodorsal nucleus of the thalamus; MDpl, mediodorsal nucleus of the thalamus, pars lateralis; MOfc, medial orbitofrontal cortex; Pf, parafascicular nucleus of the thalamus; PMA, premotor area; PN, pontine nucleus; PPN, pedunculopontine nucleus; SEF, supplementary eye field; SMA, supplementary motor area; STN, subthalamic nucleus; VA, ventral anterior nucleus of the thalamus; VAmc, ventral anterior nucleus of the thalamus, pars magnocellularis; VApc, ventral anterior nucleus of the thalamus, pars parvocellularis; Vim, ventral intermediate nucleus of the thalamus; VL, ventrolateral nucleus of the thalamus; VLcr, ventrolateral nucleus of the thalamus, pars caudalis, rostral division; VLm, ventrolateral nucleus of the thalamus, pars medialis; VLo, ventrolateral nucleus of the thalamus, pars oralis.

(^{14}C)2-deoxyglucose
A glucose analogue that is used in imaging techniques carried out on experimental animals in order to estimate the level of neural activity in specific brain regions. The (^{14}C)2-deoxyglucose is administered to the animals and subsequently taken up and trapped by active neurons.

DBS in animal models

Translational research has already transformed current DBS therapies, and a better understanding of the underlying principles of DBS gained through animal research should help us to identify safe and effective new brain targets and new stimulation paradigms for the treatment of movement and affective disorders (FIG. 4).

The MPTP-lesioned monkey model has been instrumental in developing new treatments for Parkinson's disease[64,65]. Initial studies showed that lesions of the STN in primates were efficacious and safe in alleviating the symptoms of the disease[66,67], and subsequent studies using DBS stimulation of the STN in humans showed that it was as safe and effective as GPi stimulation[68], although more psychiatric side-effects have been reported with the former, possibly due to the smaller stimulated volume[69]. The therapeutic benefits of both STN and GPi stimulation do not usually exceed those of dopaminergic medications[70], but such stimulation does have at least two advantages: reducing the required dosage of medication (and hence reducing its side effects) and reducing the duration of Parkinsonian symptoms when the medication is less effective.

This has led to the search for a target for DBS that could reduce the gait disturbances and akinesia in Parkinson's disease and potentially alleviate the akinetic symptoms and the resistance to dopaminergic medication in the late stages of Parkinson's disease, progressive supranuclear palsy and multi-system atrophy. The PPN was considered a promising target for DBS in Parkinson's disease, especially as it lies outside the basal ganglia and has no dopaminergic pathways[71].

Studies in rats and cats have shown that PPN stimulation increases movement, whereas inhibition decreases movement[72–74]. Furthermore, this region degenerates in akinetic disorders such as Parkinson's disease, progressive supranuclear palsy and multi-system atrophy. The PPN also shows increased uptake of (^{14}C)2-deoxyglucose in MPTP-treated primates[75]. This uptake is reduced following lesioning of the STN, which can reverse the primates' akinesia. Similarly, lesions of the PPN in normal primates induce akinesia[76–78]. Finally, microinjections of the GABA antagonist bicuculline into the PPN of MPTP-treated primates alleviates akinesia[79], and motor activity can be influenced by DBS of the PPN in normal primates[80], although this study used an electrode designed for human implantation and might have been confounded by stimulation of nearby structures such as the superior cerebellar peduncles.

Taken together, these studies strongly suggest that the PPN might be a potential target for alleviating Parkinson's disease, and indeed, low-frequency DBS (5–10 Hz) using a custom-made macroelectrode designed specifically for primates reversed akinesia as effectively as dopaminergic treatment in MPTP-treated monkeys[81].

Subsequent studies confirmed that stimulation of the PPN can also alleviate symptoms of Parkinson's disease in humans[82–84]. This new target offers hope of alleviating the symptoms of treatment-resistant Parkinson's disease and indeed potentially those of any patient with intractable locomotor and postural akinesia. Furthermore, the low stimulation frequencies that are required to drive the PPN could potentially extend the battery life of the pacemaker, which would greatly improve the cost-effectiveness of the treatment and perhaps even make it viable for use in developing countries.

Another example of an animal study of DBS that has come to influence clinical practice relates to the role of the nucleus accumbens in reward, and in particular in mediating 'wanting' and 'liking'[85], which has been investigated since the first self-stimulation experiments were carried out in rodents and humans in the 1950s[86,87]. Electrical and neurochemical activation of the nucleus accumbens can act as a sufficient cause of reward, as shown by elevating performance in instrumental self-administration, conditioned place preference tasks and other behavioural reward paradigms. Activation of the nucleus accumbens also elevates the hedonic impact of many natural pleasure-eliciting incentives such as food or sex[88–90]. In particular, it has been shown that opioid, endocannabinoid or related neurochemical manipulations of 'hedonic hotspots', including the nucleus accumbens and other brain regions such as the ventral pallidum, generate increases in 'liking' responses to a sensory pleasure such as sweetness[90]. This opens the possibility that DBS of the nucleus accumbens might reverse the lack of pleasure, or anhedonia, which is found in depression and other mental illnesses. Indeed, a recent study of DBS in the nucleus accumbens found a significant reduction in anhedonia in three patients with treatment-resistant depression[91]. Given the proximity of the subgenual cingulate cortex to the nucleus accumbens, this might also be a contributing factor to the positive preliminary results with DBS for treatment-resistant depression in this brain region[51]. It should, however, be noted that owing to the lack of good animal models of depression, the mechanisms that underlie these interventions are much more speculative than, for example, the targets used in Parkinson's disease.

The examples described above clearly illustrate how scientifically grounded translational research can help to bring important laboratory findings to bear on the alleviation of human suffering. Translational research can thus help us study the mechanisms that underlie the effects of DBS[16,17], the pathophysiological mechanisms and circuitries underlying the disorders[75,79] and the possible side effects of DBS[92–94].

Future perspectives

Although we do not yet have a full understanding of the mechanisms that underlie the effects of DBS, existing results are already opening up a number of exciting, new possibilities for more sophisticated stimulators, including demand-driven stimulation technologies.

An immediate and practical concern of DBS is the relatively short battery life of the stimulator, which requires surgical replacement every few years. Such surgery has many disadvantages, including the risk of infection, damage to connections, scarring and also the high cost of treatment. The introduction of externally rechargeable batteries, which are currently in development, could avoid many of these disadvantages.

Another important addition to the current applications of DBS would be the development of robust translational models of affective disorders such as depression, which is even more prevalent in the general population than movement disorders. Mood changes that are linked to alterations in reward and hedonic processing, such as unipolar depression, are found in up to 40 percent of patients with Parkinson's disease, and they often start before the onset of motor symptoms[95]. This is perhaps not surprising given the important role of the basal ganglia not only in movement, but also in affect[85]. Interestingly, several studies have shown that the STN and the PPN are also implicated in reward[96]. In fact, depression is one of the serious side-effects of STN stimulation[93], and an important future challenge is to selectively stimulate only the 'motor' part of the STN in order to avoid these affective side effects. The translational MPTP model might therefore also be useful for studying the neurocircuitry of affective disorders and developing new treatments for them (FIG. 4).

As mentioned above, the present technology in DBS equipment is at a level comparable to that of early cardiac pacemakers, and although some stimulation parameters can be altered after surgery, DBS essentially relies on open-loop continuous stimulation, with little dynamic possibility for adjustment to the individual and a high likelihood of stimulation-induced side effects. However, the possibility of recording signals from the DBS electrode opens up the prospect of developing sophisticated closed-loop variable DBS that is customized to the anatomy and morphology of the DBS target. As we come to understand the recorded neural signals better, for example, by directly measuring signals from externalized electrodes and correlating these with whole-brain activity as measured by MEG, it is likely that we will find certain neural 'signatures' of pathological brain activity[20]. Such neural signatures might then help to drive closed-loop demand-driven stimulators[97]. The development of such devices will obviously require a detailed understanding of normal oscillatory brain activity, which may be provided by neuroimaging studies and sophisticated computer models of neural activity.

This research opens up the possibility for more general, advanced brain–computer interfaces, which might be useful for patients in numerous pathological states and, for example, might help patients with spinal cord injuries in learning to control their limbs or prostheses. DBS-driven brain–computer interfaces might in the future modulate brain activity in order to help individuals in vegetative and minimally conscious states[98].

Until such times, from a systems neuroscience point of view, it is the causal and interventional nature of DBS that is particularly exciting. The combined use of DBS and whole-brain neuroimaging methods like MEG has the makings of a powerful and sophisticated tool for unravelling the fundamental mechanisms of normal and abnormal human brain function.

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