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DEEP BRAIN STIMULATION

Sing the mind electric – principles of deep brain stimulation

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Abstract

The remarkable efficacy of deep brain stimulation (DBS) for a range of treatment-resistant disorders is still not matched by a comparable understanding of the underlying neural mechanisms. Some progress has been made using translational research with a range of neuroscientific techniques, and here we review the most promising emerging principles. On balance, DBS appears to work by restoring normal oscillatory activity between a network of key brain regions. Further research using this causal neuromodulatory tool may provide vital insights into fundamental brain function, as well as guide targets for future treatments. In particular, DBS could have an important role in restoring the balance of the brain's default network and thus repairing the malignant brain states associated with affective disorders, which give rise to serious disabling problems such as anhedonia, the lack of pleasure. At the same time, it is important to proceed with caution and not repeat the errors from the era of psychosurgery.

Introduction

The American poet Walt Whitman wrote his poem 'I sing the body electric' in the middle of the 19th century, as scientific studies were starting to uncover the importance of electricity in biological species. Since then, the electrical nature of the body – and of the brain – has been confirmed by an abundance of scientific research. As we have come to better understand the functional neuroanatomy of the brain, it has become clear that there is very little that goes wrong that could not, hypothetically, benefit from finely calibrated pulses of electricity.

Deep brain stimulation (DBS) is one of the most promising neuromodulatory techniques available today, and has over the last couple of decades shown remarkable clinical efficacy and safety in helping with many brain-related problems, such as movement disorders and chronic pain (Kringelbach *et al.*, 2007b; Montgomery & Gale, 2008). Near miraculous improvement in the symptoms of many patients has captured the attention of the general public, and spurred by these findings, psychiatrists around the world have started to use DBS for the treatment of psychiatric disorders, such as depression and obsessive-compulsive disorders (Kopell & Greenberg, 2008).

But the remarkable clinical efficacy and long history of DBS has not been matched by a comparable scientific understanding of the underlying principles and neural mechanisms. What is clear from translational research is that DBS directly changes brain activity in a controlled manner and that, in principle, the resulting effects are reversible.

We first review some of the relevant translational experimental evidence from neurophysiology, neuropharmacology and neuroimaging data from a variety of mammals that are relevant for trying to understand the underlying mechanisms of human DBS. This is synthesized into a neural and systems-level model for DBS, which can explain some of the available data. We then demonstrate how such translational research has led to novel DBS targets for Parkinson's disease, specifically addressing the recent promising development of a new target in the brainstem nucleus, the pedunculopontine nucleus (PPN). This naturally leads to a discussion of recent progress in applying DBS for affective disorders, and we discuss the potential of DBS in restoring the balance of the brain's default networks. Finally, we further explore some of the future perspectives for refining and expanding the use of DBS.

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Principles of DBS

In order to understand how DBS functions, it is paramount that we first improve our understanding of how brain regions oscillate and communicate (Schnitzler & Gross, 2005). This knowledge is most likely to come through translational models, as has been the case with Parkinson's disease, where the highly successful 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model has helped to understand the pathophysiology of Parkinson's disease (Langston *et al.*, 1983). This also helped identify potential targets, such as the subthalamic nucleus (STN; Bergman *et al.*, 1990; Aziz *et al.*, 1991), which was subsequently shown to be an efficacious DBS target in monkeys (Benazzouz *et al.*, 1993), and subsequently in humans (Weaver *et al.*, 2009).

In a healthy brain, neurons in the basal ganglia communicate back and forth in an intricate call and response with groups of neurons in other brain areas, including the thalamus and the motor cortex (McIntyre & Hahn, 2010). All these brain areas play a role in movement, and must work together for movement to be quick and fluid. These oscillations of neural activity bounce back and forth, moving at different frequencies, some serving to initiate movement,

others to moderate it, but what is key is that the sender and recipient neurons, like two girls rhythmically swinging a jump rope for a third to hop over, must be in sync (Fig. 1).

In Parkinson's disease, diseased neurons lose their ability to keep up, and the oscillations become unbalanced. Human studies have found that there are strong increases in beta (15–30 Hz) oscillatory activity in the STN when the patients were without dopaminergic medication, while therapeutic effective STN stimulation of more than 70 Hz suppresses activity in the basal ganglia in the beta band at about 20 Hz (Brown *et al.*, 2004).

Yet, the causal links between these aberrant oscillations, disruptions of dopaminergic transmission and parkinsonian motor signs are not fully understood. Findings in rodents have shown that the amplified beta oscillations are delayed sequelae of chronic dopamine depletion (Mallet *et al.*, 2008). Similarly, progressive dopamine depletion in two non-human primates led to severe akinesia, rigidity and postural abnormalities, but spontaneous firing rates did not vary significantly after intoxication. Synchronous oscillatory activity appeared only after major motor symptoms developed, casting doubt on the causal links between the emergence of synchronous oscillations and main parkinsonian motor symptoms (Leblois *et al.*, 2007).

All of this raises important questions of how the important therapeutic effects of DBS are achieved. Fundamentally, DBS of the normal and diseased brain must fundamentally depend on the interaction between the stimulation and the functional neuroanatomy of the brain. We will briefly discuss some of the features of the three main factors: (i) stimulation parameters including amplitude and temporal characteristics; (ii) the physiological properties of the brain tissue, which may change with disease state; and (iii) the interactions between the deep brain electrode and the surrounding tissue arising from the specific geometric configurations.

The relative contribution of these three factors to the underlying mechanisms of DBS have been assessed experimentally in humans and other animals through direct neurophysiological recordings (Dostrovsky *et al.*, 2000; Anderson *et al.*, 2003; Hashimoto *et al.*, 2003; Pralong *et al.*, 2003; Brown *et al.*, 2004), neurochemistry (Windels *et al.*, 2000; Boulet *et al.*, 2006) and functional neuroimaging methods (Perlmutter *et al.*, 2002; Hershey *et al.*, 2003;

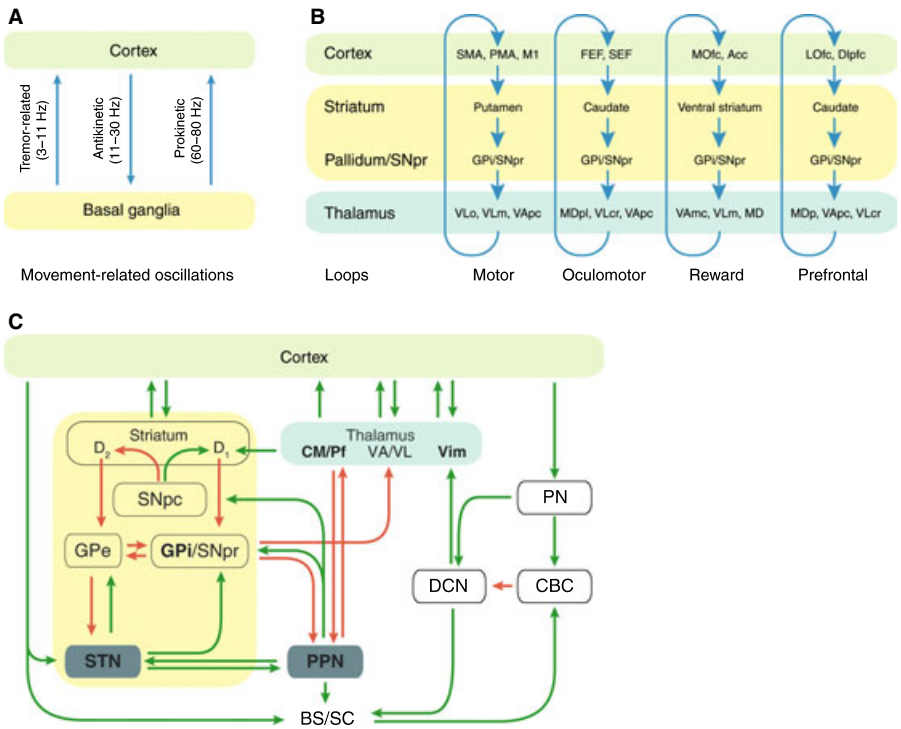

FIG. 1. DBS, oscillations and brain networks. (A) Schematic figure of movement-related oscillations in Parkinson's disease. Pathological oscillations arise in basal ganglia-cortical systems, which can be restored with DBS in select nuclei (see structures written with bold letters in C). Rest-tremor-related activity with frequencies of 3–11 Hz arises in the basal ganglia and spreads to the cortex. The subthalamic nucleus (STN) is driven by antikinetic oscillations in the beta band (11–30 Hz) in the cortex, while oscillations in the gamma band (60–80 Hz), which facilitate movement (prokinetic), are suppressed or absent in Parkinson's disease. (B) There are many important segregated parallel thalamocortical circuits, including the motor, oculomotor, reward and prefrontal loops, which play key roles in movement and affective disorders. (C) Translational research has given rise to a better understanding of the detailed circuitry of the basal ganglia, which has been important for the discovery of two targets (dark blue) for the DBS treatment of the symptoms of Parkinson's disease. 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 pathways, the activity of which is controlled by the substantia nigra pars compacta (SNpc): a direct D1 receptor-mediated pathway to the internal globus pallidus (GPi)/substantia nigra pars reticulate (SNpr); and an indirect D2-receptor-mediated pathway involving the external globus pallidus (GPe) and the STN. The former pathway is thought to facilitate movement, while the latter is thought to suppress movement through activity in specific frequency bands. The GPi and SNpr send inhibitory output to the thalamus. DBS of select regions of the basal ganglia (bold) has been shown to restore some of the symptoms of Parkinson's disease. Green arrows indicate excitatory (glutamatergic) pathways, and red arrows indicate inhibitory (GABAergic) pathways. Future challenges include a better understanding of the nature of the oscillations in these movement-related networks and how they relate to other networks such as the prefrontal and reward. Abbreviations: Acc, anterior cingulate cortex; BS/SC, brain stem/spinal cord; CBC, cerebellar cortex; CM, centromedian nucleus of thalamus; DCN, deep cerebellar nuclei; Dlpfc, dorsolateral prefrontal cortex; FEF, frontal eye fields; Lofc, lateral orbitofrontal cortex; M1, primary motor cortex; MDpl, mediodorsal nucleus of thalamus, pars lateralis; Mofc, medial orbitofrontal cortex; Pf, parafascicular nucleus of the thalamus; PMA, premotor area; PN, pontine nucleus; SEF, supplementary eye field; SMA, supplementary motor area; VA, ventral anterior nucleus of thalamus; VAmc, ventral anterior nucleus of thalamus, pars magnocellularis; VApc, ventral anterior nucleus of thalamus, pars parvocellularis; Vim, ventral intermedius nucleus of the thalamus; VL, ventrolateral nucleus of thalamus; VLcr, ventrolateral nucleus of thalamus, pars caudalis, rostral division; VLm, ventrolateral nucleus of thalamus, pars medialis; VLo, ventrolateral nucleus of thalamus, pars oralis.

Kringelbach *et al.*, 2007a; Ballanger *et al.*, 2009a). Furthermore, computational modelling has been used to predict and test the effects of DBS (Durand, 2003; McIntyre *et al.*, 2004a).

The 'stimulation parameters' of therapeutic value have come about primarily by trial and error by using the almost immediate effects in patients on the operating table (Volkmann *et al.*, 2002). Examples of such effects include changes in tremor, rigidity, paresthesia, bradykinesia and chronic pain. The exact DBS parameters vary with treatment and targeted brain region, but are usually between 1 and 9 V stimulus amplitude; 60 and 240 μs stimulus pulse duration; monopolar cathodic; and either low (5–50 Hz) or high (130–180 Hz) stimulus frequencies (Kuncel & Grill, 2004). It is obviously important to have the necessary safeguards to prevent tissue damage, and *post mortem* studies have shown that a charge-density limit of 30 $\mu C/cm^2$ should be used (Kuncel & Grill, 2004). Most commercially available stimulators will allow for the stimulation parameters to be changed and fine-tuned over time, but based solely on the patient's behavioural state (Coffey, 2008). The technology is open-loop continuous stimulation, which cannot be adjusted real-time to the continuous changes in brain state of the individual patient, but we will return to this issue later.

The 'physiological properties' of normal and diseased brain tissue have variable electrical properties depending on the types of neurons and supporting glial cells that utilize different types of ion channels with variable voltage-sensitive properties. The most excitable neural elements are the myelinated axons (Ranck, 1975; McIntyre *et al.*, 2004a). DBS has different effects on the various neural elements depending on the non-linear relationship between stimulus duration (pulse width) and amplitude (voltage or current) necessary to stimulate the neural element (Ranck, 1975). The minimal current necessary to stimulate a neural element with a long stimulus duration is called 'rheobase', which is the amplitude threshold. The 'chronaxie' time measurement is the minimum interval of time required to excite a neural element using twice the intensity that elicits a threshold response (Fig. 2A). Myelinated axons have chronaxies of about 30–200 μs, while the chronaxies of cell bodies and dendrites are about 1–10 ms, and thus substantially larger (Holsheimer *et al.*, 2000). This makes it most likely that the postsynaptic responses resulting from normal DBS parameters are the result of activity from efferent and afferent axons, as well as passing fibres, rather than from cell bodies (Nowak & Bullier, 1998b). This in turn allows DBS to modulate the activity of remote neural structures both in terms of excitation and inhibition.

The 'geometric configuration of neural elements' in relation to the electrode is important for determining the effects of stimulation on local and global neural elements. It has been shown that the orientation of the axons and the cell body is an important determinant of neural responsiveness (Ranck, 1975). The distance of the neural elements from the electrode is also an important factor – both the rheobase and chronaxie rising in proportion to distance, such that the responsiveness of more distal elements is increasingly unlikely (Holsheimer *et al.*, 2000). The stimulation volume is not a fixed cylinder around the stimulation electrode, but varies with electrode position and surrounding neural tissue. Normal clinical DBS parameters lead to the stimulation of a large volume of neural tissue (Durand, 2003; McIntyre *et al.*, 2004a). For example, modelling the excitability effects for STN stimulation using realistic white-matter pathways has shown that the stimulation can spread outside the STN proper, and the pattern of excitation is consistent with known stimulation side-effects (Durand, 2003). Currents from monopolar cathodes of more than eight times threshold may block action potentials in axons in all likelihood due to hyperpolarization (Garcia *et al.*, 2005). STN DBS can lead to a change in the discharge pattern of STN neurons by reducing the spontaneous activity while at the same time producing recurrent bursts of spikes time-locked to the stimulus (Garcia *et al.*, 2003).

The data show that the effects of high-frequency DBS are complex, and can cause both inhibition and excitation (Liu *et al.*, 2008). The most effective stimulation from an electrode is not necessarily in nearby neural elements immediately adjacent to the electrode – or in more distal neural elements. Instead, the most effective DBS could be affecting intermediate neural elements, which are then helping to modulate more remote mono- and polysynaptic connected brain structures.

Neurophysiological recordings

Evolution appears to have preserved many of the general principles for neural processing across species, and thus data from other species such as rats and non-human primates are relevant for understanding the mechanisms of DBS. We will briefly concentrate here on *in vivo* studies in higher primates (Kringelbach *et al.*, 2007c; Miocinovic *et al.*, 2007, 2009), while we will not discuss the results of the many studies in rodents, of which there are other good reviews (Perlmutter & Mink, 2006).

A number of research groups have used MPTP-treated primates to study both the local and distal effects of stimulation. Take for example the effects of STN stimulation on activity in neurons in the globus pallidus (GP; Hashimoto *et al.*, 2003; Kita *et al.*, 2005). High-frequency STN stimulation was found to cause activation in STN efferent fibres, while the multiphasic response patterns found are suggestive of mono- and polysynaptic activity in other parts of the basal ganglia (Hashimoto *et al.*, 2003). Similar results were found in the study using single STN stimulation, which induced a short-latency excitation followed by a weak inhibition on neurons in globus pallidus externa (GPe), and a short-latency, very short-duration excitation followed by a strong inhibition in neurons in globus pallidus interna (GPi). These findings suggest that more complex polysynaptic responses dominate over monosynaptic responses in the GPi (Kita *et al.*, 2005).

Similarly, recordings of thalamic activity in response to high-frequency GPi stimulation in normal, awake monkeys found that GPi stimulation asserts not only local effects but also has direct effects on efferent axons. The stimulation changes baseline firing rates, and disrupts normal and abnormal task-related patterns of activity in postsynaptic neurons (Anderson *et al.*, 2003).

Human studies of distal effects of stimulation are more rare, as most studies have primarily used local rather than distal neurophysiological recordings. Distal recordings were used in a study in a dystonic patient who had previously undergone a non-beneficial DBS GPi implantation and was subsequently implanted with thalamic DBS. The patient was anaesthetized during GPi stimulation and the recording of activity in thalamic neurons (Pralong *et al.*, 2003). Consistent with the previous findings in monkeys (Anderson *et al.*, 2003), the majority of the tonically active thalamic neurons were inhibited, while the activity of the rest of the low-frequency neurons remained unchanged.

As mentioned earlier, recordings of local field potentials (LFPs) from the STN in patients with Parkinson's disease after neurosurgery found strong increases in beta (15–30 Hz) oscillatory activity in the STN when the patients were without dopaminergic medication, which were subsequently suppressed with both medication (Brown *et al.*, 2001) and therapeutic effective STN stimulation of more than 70 Hz (Brown *et al.*, 2004).

This suggests that some symptoms of Parkinson's disease might be linked to an abnormal and potentially deleterious synchronization of basal ganglia output in the beta frequency band of about 20 Hz (Hammond *et al.*, 2007). It also strongly suggests that for movement

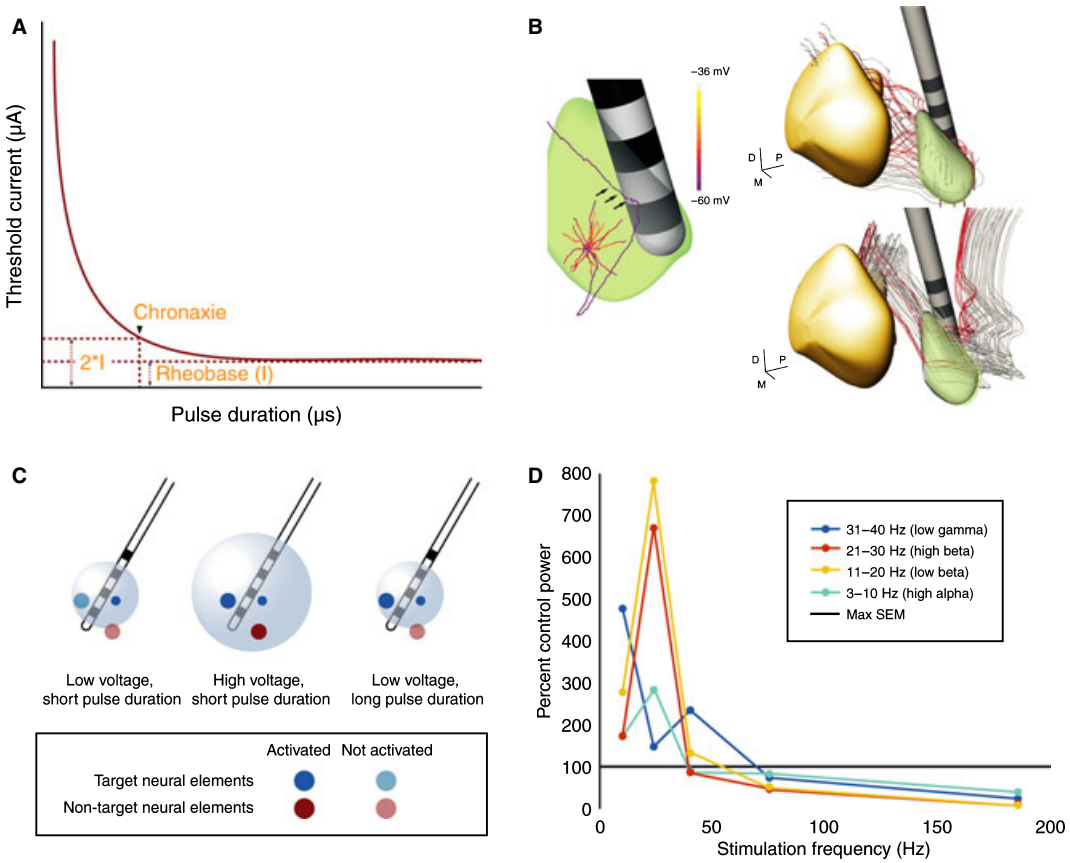

FIG. 2. DBS of brain tissue and networks. (A) The pulse duration and threshold current necessary to stimulate a neural element have a non-linear relationship. As can be seen from the figure, the rheobase (I, measured in microamperes) corresponds to the horizontal asymptote in the strength–duration curve, while the chronaxie (measured in μs) is defined as the duration of the threshold current pulse having an intensity twice that of the rheobase. Typical values for the chronaxie are about 30–200 μs for myelinated axons, and about 1–10 ms for cell bodies and dendrites. Myelinated axons are thus the most likely neural elements to be affected by DBS (Ranck, 1975; Nowak & Bullier, 1998a). (B) This was confirmed in a computational model of the effects of DBS in the STN (coloured light green) and GPi (coloured light yellow). The DBS electrode typically has four leads (black bars) separated by between 0.5 and 1.5 mm, depending on the type. The figure on the left shows a 3D reconstruction of a field-neuron model of STN DBS, where extracellular potentials generated by the electrode create transmembrane polarization along the STN projection neuron. The neural compartments are coloured according to their transmembrane potential at the onset of a subthreshold stimulus pulse (the neural processes have been thickened for figure rendering). The arrows indicate the depolarized nodes of Ranvier. The right figures show the neural activation during clinically effective DBS in STN axons (top) and GPi fibres (bottom) shown in red, where the axons that did not respond to over 80% of the stimulus pulses are shown in grey. This shows how the output of STN stimulation can result in the spread of activation to STN axons and GPi fibres, which in turn can generate specific changes in oscillatory neural activity between the cortex and the basal ganglia (Miocinovic *et al.*, 2006, 2007). (C) The schematic, yet practical effects of the relationship between voltage and pulse duration on neural elements are shown. DBS with low voltage activates only some of the target neural elements (dark blue), while most target (light blue) and all non-target neural elements (light red) are not activated. Increasing the voltage will activate both target and non-target elements (dark red), while increasing the pulse duration will activate target but not non-target elements. (D) Human studies have demonstrated that therapeutic high-frequency STN stimulation for Parkinson's disease works through suppression of the malignant changes in beta band oscillations in the basal ganglia. The results show that LFP power frequencies below 40 Hz are suppressed by therapeutic high-frequency DBS (> 75 Hz), while this is not true for non-therapeutic stimulation (25 Hz; Brown *et al.*, 2004).

disorders DBS stimulation could work through reducing malignant oscillations in the beta band in the closed loop networks involved in motor control – although it should be stressed again that the links between malignant oscillations, disruptions of dopaminergic transmission and parkinsonian motor signs are not fully understood. It is also important to realise the inherent complexity of the DBS effects in movement disorder, which can extend beyond the motor circuits into other domains through the multiple segregated parallel thalamocortical circuits (Fig. 1B; Alexander *et al.*, 1986).

Functional neuroimaging

Unlike neurophysiological studies, functional neuroimaging methods allow for the study of the whole-brain activity elicited by DBS. The most widespread of these neuroimaging methods are positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), which can measure indirect changes of neural activity, such as blood flow, blood oxygenation and glucose consumption. Presently it is not, however, clear how well these indirect measurements correlate with various aspects of neural activity, but some progress has been made under normal physiological conditions (Logothetis & Wandell, 2004; Lauritzen, 2005).

In addition, fMRI studies clearly pose a large degree of risk to DBS patients, as the large magnitude of the magnetic fields will interfere with active pulse generators and DBS electrodes. One study showed that extreme caution must be exercised when studying DBS with fMRI as strong heating, high induced voltage and even sparking at defects in the connecting cable have been observed (Georgi *et al.*, 2004). It has also been shown that fMRI using the blood-oxygen level-dependent (BOLD) signal as a measurement may be problematic, as near-infrared spectroscopy showed considerable variations in blood oxygenation in the frontal cortex following GPi and thalamic stimulation (Sakatani

et al., 1999). Despite these important caveats, a case report has been published using fMRI to study STN stimulation in a patient with Parkinson's disease. The results showed increases in the BOLD signal in primary motor areas and decreases in supplementary motor areas during STN stimulation (Stefurak *et al.*, 2003).

Similarly, PET is not without health risks due to the ionized radiation, but has been used for measuring the effects of DBS. It should be noted, however, that the long acquisition times (on the scale of minutes) make the ensuing brain changes difficult to interpret, and investigators have to carefully address the potential movement artefacts when studying movement disorders.

Several PET studies have taken the necessary precautions to study the effects of DBS in movement disorders. In a group of patients with Parkinson's disease, STN stimulation led to increased blood flow in the thalamus, GP and midbrain (including STN), and reduced blood flow in frontal parietal and temporal cortices (Hershey *et al.*, 2003). Similarly, a PET study of ventral intermedius nucleus of the thalamus (Vim) stimulation in patients with essential tremor showed increases in blood flow in the thalamus and the cortical targets of thalamic output (Perlmutter *et al.*, 2002).

Using PET to study DBS for affective disorders is less challenging in terms of potential movement artefacts. One PET study investigated the effects of hypothalamic stimulation for cluster headache in 10 patients (May *et al.*, 2006) and found that hypothalamic stimulation modulated the pain-processing network (Grover *et al.*, 2009). Another PET study used stimulation of subgenual cingulate cortex for treatment-resistant depression, of which four out of six patients showed marked reduction in mood symptoms (Mayberg *et al.*, 2005). The results are harder to interpret given the small numbers of patients and the paucity of knowledge about the brain structures involved in depression, but suggest that the mode of functioning of DBS would appear one of modulating an existing network of interacting brain regions.

In contrast to PET and fMRI, magnetoencephalography (MEG) is non-invasive and almost without risks for use in patients, and can provide novel spatiotemporal information on the underlying whole-brain activity, with the current density of MEG sensors affording sensitivity such that the spatial resolution is comparable to fMRI (typically about 5 mm^3), but with much better temporal resolution (in ms; Hillebrand & Barnes, 2002; Hansen *et al.*, 2010). A subsequent study used simultaneous LFP and MEG to show that beam-forming is capable of suppressing the high-amplitude artefacts caused by the DBS wire and electrode, and extracting artefact-free virtual electrode time-series (Litvak *et al.*, 2010). Using beam-former source reconstruction for the coherence pattern, they found maximum coherence between the LFPs recorded from the STN and activity in the premotor cortex.

The first MEG study of DBS was carried out in a patient with low-frequency periventricular/periaqueductal grey (PVG/PAG) stimulation for severe phantom limb pain (Kringelbach *et al.*, 2006, 2007a). 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, including the mid-anterior orbitofrontal and subgenual cingulate cortices; these areas are known to be involved in pain relief (Kringelbach, 2005). Similarly, MEG of high-frequency hypothalamic stimulation for cluster headache showed a similar pattern of changes in neural activity in a widespread cortical and sub-cortical network, including the orbitofrontal cortex (Ray *et al.*, 2007). Due to its non-invasive nature and high spatial and temporal resolution, MEG holds great promise in elucidating the underlying whole-brain neural mechanisms of DBS by, for example, measuring oscillatory communication between brain regions (Schnitzler & Gross, 2005).

Synthesis of mechanisms

The experimental evidence collected so far allows for some conclusions to be drawn about the neural and systems level mechanisms of action of DBS. The effects of DBS do vary with the stimulation parameters (including frequency, amplitude, pulse width and duration); with the intrinsic physiological properties; and with the interactions between the electrode and the geometric configuration of the surrounding neural tissue and specific anatomy of the targeted region. The evidence clearly shows that DBS affects multiple neural elements, but foremost myelinated axons and to a lesser degree cell bodies.

The weight of the evidence has shown that the most likely mode of action for DBS is through stimulation-induced modulation of brain activity (Montgomery & Baker, 2000; Vitek, 2002; McIntyre *et al.*, 2004b; Kringelbach *et al.*, 2007b; McIntyre & Hahn, 2010), rather than competing hypotheses such as synaptic inhibition (Dostrovsky *et al.*, 2000), depolarization blockade (Beurrier *et al.*, 2001) or synaptic depression (Urbano *et al.*, 2002).

Supporting the importance of the cortical afferents to STN, a STN–DBS study in rats showed that antidromic resonant activation of cortical microcircuits helps counteract the malignant oscillatory activity found in Parkinson's disease (Li *et al.*, 2007). The amplitude of antidromic activation was significantly correlated with suppression of slow-wave and beta band activity during STN–DBS. Further optogenetic experiments in rodents support this conclusion by showing that therapeutic effects within the STN can be accounted for by direct selective stimulation of afferent axons projecting to this region (Gradinaru *et al.*, 2009).

The similar therapeutic effects of DBS and lesioning are thus likely to be achieved through different mechanisms. The modulation is likely to come about through the local effects of the DBS electrode on the neural activity in the DBS target, which is passed on to mono- and polysynaptic network connections. Taking STN stimulation as an example (McIntyre *et al.*, 2004b), near the electrode a small volume of the applied field will activate projection neurons, and a larger volume will activate afferent inputs, while projection neurons in the volume formed by the difference between these two volumes are suppressed by the stimulation-induced trans-synaptic inputs. The output of STN stimulation will thus result in high-frequency glutaminergic inputs to GPe and GPi, and it is possible that many neurons in GPe will be antidromically activated through their afferent inputs in STN (Hashimoto *et al.*, 2003). Further spread of activation to GPi axons and the lenticular fasciculus are also likely, which in turn can generate specific changes in the oscillatory neural activity between the cortex and the basal ganglia. This is supported by studies that 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 (Brown *et al.*, 2004).

Overall, the data suggest that for movement disorders DBS works by modulating the larger, closed loop networks of thalamocortical and corticostriatal connections, where sequential motor program commands are setup, passed on and executed (Leblois *et al.*, 2006; Li *et al.*, 2007). Movement disorders can be conceptualized as subtle shifts or corruption of this distributed spatiotemporal information and, as suggested by computational modelling, DBS works by specifically regularizing diffuse but functionally related networks (McIntyre & Hahn, 2010).

Translational research

Current DBS therapies have already been transformed by translational research, which may also help to identify safe and effective new brain targets as well as new stimulation paradigms to treat movement and affective disorders.

New treatments for Parkinson's disease have used rodent models as well as the MPTP model in primates (Burns *et al.*, 1983; Langston *et al.*, 1983). Initially, lesions of the STN in primates were shown to be efficacious and safe in alleviating the symptoms of Parkinson's disease by two research groups at roughly the same time (Bergman *et al.*, 1990; Aziz *et al.*, 1991). Subsequent DBS STN in the MPTP primate was also successful (Benazzouz *et al.*, 1993). Similarly, human studies using DBS stimulation of STN have been shown to be as safe and efficacious as GPi stimulation (Limousin *et al.*, 1995), although there are more known psychiatric side-effects with STN stimulation. This is possibly due to the fact that the STN is a smaller volume than the GPi, and that STN stimulation may also involve non-motor regions of the STN and adjacent areas (Voon *et al.*, 2005). The therapeutic benefits of both STN and GPi stimulation do not usually exceed those of dopaminergic medications (Pahwa *et al.*, 2005), but they have at least two main advantages: reducing medication and its side-effects; and reducing the time spent with parkinsonian symptoms when the medication is less effective.

This led us to search for a target that could also help with the gait disturbances and akinesia in Parkinson's disease, and potentially alleviate the resistance to dopaminergic medication and akinetic symptoms in the late stages of Parkinson's disease, progressive supranuclear palsy and multi-system atrophy. The PPN had emerged over a number of years as a promising target for DBS in Parkinson's disease (Jenkinson *et al.*, 2009), especially as it lies outside the basal ganglia – although it has been argued that it should be considered as an integral part (Mena-Segovia *et al.*, 2004). The majority of cells in the PPN express acetylcholine (Mesulam *et al.*, 1989; Mena-Segovia *et al.*, 2008), but there are many cells within the PPN that utilize other neurotransmitters, including glutamate (Clements & Grant, 1990), γ-aminobutyric acid (GABA; Ford *et al.*, 1995; Mena-Segovia *et al.*, 2009) and dopamine (Rye *et al.*, 1987; Rolland *et al.*, 2009).

Animal studies in rats and cats had shown that stimulation of the PPN increases and inhibition decreases movement (Brudzynski *et al.*, 1986; Garcia-Rill *et al.*, 1987; Mogenson & Wu, 1988), and that this region degenerates in akinetic disorders such as Parkinson's disease, progressive supranuclear palsy and multi-system atrophy. PPN also shows increased uptake of labelled 2-Deoxy-D-glucose (2-DG) in MPTP-treated primates (Crossman *et al.*, 1985). This uptake is reduced after STN lesions, which can reverse akinesia in MPTP-treated primates. This is similar to the effects of lesions of the PPN in normal primates, which can induce akinesia (Kojima *et al.*, 1997; Aziz *et al.*, 1998; Munro-Davies *et al.*, 2001).

Following these studies, we showed that microinjections of the GABA antagonist bicuculline into the PPN of MPTP-treated primates can alleviate akinesia (Nandi *et al.*, 2002a). We also showed that motor activity can be influenced by DBS in the PPN in normal primates (Nandi *et al.*, 2002b), 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.

These studies strongly suggested that the PPN might be a potential target for alleviating Parkinson's disease, and we therefore implanted a custom-made macroelectrode designed specifically for primates. We found that low-frequency DBS (5–10 Hz) reversed akinesia as effectively as dopaminergic treatment (Jenkinson *et al.*, 2004).

Subsequent human studies have confirmed that stimulation of the PPN is effective in alleviating symptoms related to gait and postural disorders found in patients with Parkinson's disease (Mazzone *et al.*, 2005; Plaha & Gill, 2005; Stefani *et al.*, 2007). This target offers hope of alleviating the symptoms of treatment-resistant Parkinson's disease and indeed potentially any patient with intractable locomotor and postural akinesia, as confirmed by a neuroimaging study of PPN patients (Ballanger *et al.*, 2009b). Recent findings have also suggested that stimulation of the PPN may alleviate aspects of non-motor problems in Parkinson's disease, such as sleep quality and cognitive performance (Alessandro *et al.*, 2010; Stefani *et al.*, 2010). Finally, the low stimulation frequencies required to drive the PPN could potentially extend the battery life of the pacemaker, which will greatly improve the cost effectiveness of the treatment. Yet, a larger patient population is clearly needed to fully evaluate the efficacy of PPN stimulation.

Translational research can thus help us study the mechanisms that underlie the effects of DBS, the pathophysiological mechanisms and circuitries underlying the disorders, as well as the possible side-effects of DBS. The example given above of the identification of the PPN target clearly illustrates how scientifically grounded translational research can help to bring important laboratory findings to bear on the alleviation of human suffering.

The brain's default networks and the alleviation of anhedonia

The lack of pleasure, anhedonia, is one of the most important symptoms of many mental illnesses, including depression and schizophrenia (Gorwood, 2008). The success of DBS in alleviating the symptoms of movement disorders has prompted psychiatrists to start using DBS for affective disorders, yet it is clear that this is much more difficult as there are few, if any, effective translational animal models.

We have previously argued that the MPTP model may also be useful (Kringelbach *et al.*, 2007b), as many of the brain structures involved in movement disorders are also implicated in affective disorders as, for example, demonstrated by how severe depression can be reversibly induced by DBS for Parkinson's disease (Bejjani *et al.*, 1999; Temel *et al.*, 2006). The ethical implications of DBS for the treatment of affective disorders should be carefully considered to avoid comparisons to the psychosurgery of last century (Kringelbach & Aziz, 2009; Sachdev & Chen, 2009; Schiff *et al.*, 2009; Biswal *et al.*, 2010).

Yet, it is over 50 years since chronic pain started to be treated by stimulation in the hypothalamus (Pool *et al.*, 1956). More recent efficacious targets have been found in the thalamus (Mazars *et al.*, 1960, 1973; Hosobuchi *et al.*, 1973) and the PVG/PAG region (Hosobuchi *et al.*, 1977; Richardson & Akil, 1977a,b,c). Following two failed clinical trials, FDA approval was not sought, however, by device manufacturers. During the last decade only five centres outside the USA have produced case series of more than six patients. These studies have shown significant improvements for patients with primarily pain after amputation and stroke, and head pain including anaesthesia dolorosa (Kringelbach *et al.*, 2009). Patients with cluster headache have been successfully treated with DBS in the hypothalamus (Franzini *et al.*, 2003; Leone *et al.*, 2004; Grover *et al.*, 2009).

In parallel to these treatments for pain, other affective disorders have started to be treated with DBS. This includes treatment-resistant depression, where targets have included thalamus (Andy & Jurko, 1987; Jimenez *et al.*, 2005) and the subgenual cingulate cortex (Mayberg *et al.*, 2005). DBS in the nucleus accumbens has also been found to give a significant reduction in anhedonia and anxiety in patients with treatment-resistant depression (Schlaepfer *et al.*, 2008; Bewernick *et al.*, 2010). DBS for obsessive-compulsive disorder has targeted the anterior internal capsule (Nuttin *et al.*, 2003), while DBS of the thalamus (Visser-Vandewalle *et al.*, 2003) and GPi (Ackermans

et al., 2006) have been reported to be effective in treating Tourette's syndrome.

At the present time it is not clear why and how these DBS targets work, but the causal nature of DBS must mean that these targets interact with the brain's resting state networks, which are the steady state circuits of the brain (Lou *et al.*, 1999; Gusnard & Raichle, 2001; Biswal *et al.*, 2010; Fig. 3). Functions of the default network and associated resting state networks include self-awareness, remembering the past and prospecting the future (Addis *et al.*, 2007). We have previously proposed that the default network, and related neural circuits, contribute to computing relations between self and others, evaluating eudaemonic meaning and interacting with hedonic circuits of positive affect (Kringelbach & Berridge, 2009).

Future challenges for DBS include how to best restore the balance of these resting networks in malignant disorders (Giacobbe *et al.*, 2009). The frontal parts of the resting state networks include regions such as the medial prefrontal and orbitofrontal cortex, which are known to modulate hedonic state (Kringelbach, 2005). One possible hypothesis is thus that DBS for affective disorders could work by modulating the hedonic circuitries to alleviate anhedonia (Kringelbach & Berridge, 2009).

We made a tentative start to understand how the lack of pleasure can be directly influenced by DBS. We used MEG to investigate how a DBS electrode implanted in the PVG/PAG region can help a wider network alleviate the suffering of chronic pain (Kringelbach *et al.*, 2007a), and found that stimulation in the PVG/PAG region elicited activity in regions including the mid-anterior orbitofrontal cortex, which we have identified as a key component of the pleasure network in the human brain (Kringelbach, 2005).

Future directions

DBS is an important tool both for alleviating human suffering and for obtaining novel insights into the nature of fundamental brain function. Due to the existence of the robust MPTP translational model, DBS has so far proven most useful for controlling movement disorders. It is, however, imperative to find novel ways to treat affective disorders such as depression, which are far more prevalent than movement disorders in the general population (Kringelbach, 2005). We have previously suggested that translational research using DBS and the MPTP model in primates may also be useful for the treatment of affective disorders given the role of the basal ganglia not only in movement but also in affect (Kringelbach *et al.*, 2007b).

Other innovations such as closed-loop demand-driven stimulators have great potential for transforming the therapeutic potential of DBS. Through the use of MEG and DBS we will come to understand the normal oscillatory activity of specific brain regions better (Brown *et al.*, 2004), and such 'neural signatures' may come to help drive specific DBS interventions.

We now have potential evidence of such a neural signature of pain in DBS patients who showed characteristically enhanced low-frequency (8–12 Hz) power spectra of both PVG/PAG and ventral posterior lateral and medial (VPL/VPM) LFPs when in pain (Green *et al.*, 2009). Further research is required to elucidate if such neural signatures could aid patient selection, in particular if combined with technical advances in MEG to characterize whole-brain functional neuronal connectivity.

In general, such research on feedback-driven neural prostheses may open up for more advanced brain–computer interfaces, which can in time come to help patients in a number of pathological states (Lee *et al.*, 2009).

Overall, DBS is a remarkable therapeutic tool, which has great future potential both in terms of improving clinical efficacy and in terms of understanding the fundamental mechanisms of normal human brain function.

On this evidence DBS can indeed sing the mind electric, and there is a sense of great expectancy in the air. Yet, as we probe the 3 lb of wrinkled flesh that houses a human consciousness, it is important that we proceed with a combination of humility and hubris. While tinkering with the very core of what makes us human, we must not forget the lessons from psychosurgery of the last century and clear ethical guidelines must guide future experiments.

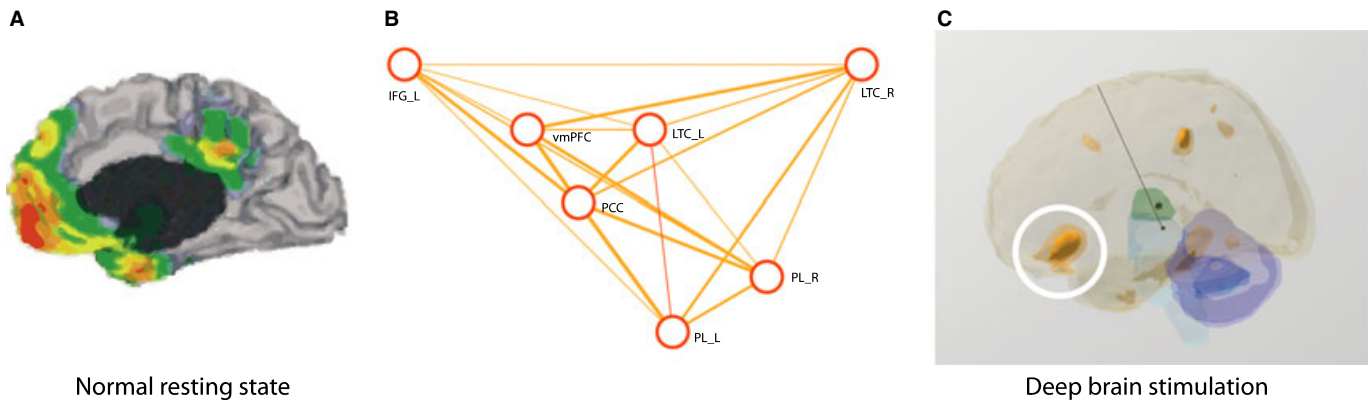

FIG. 3. DBS and the resting state networks. (A) DBS causally alters brain activity and as such it must be linked to the brain's default network, which is a steady state circuit of the brain (Gusnard & Raichle, 2001) that has been linked to self-awareness, remembering the past and prospecting the future (Addis *et al.*, 2007). Some of the components of the default network include midline structures such as the orbitofrontal, medial prefrontal and cingulate cortices, which are involved in pleasure, reward and affective disorders (Kringelbach & Berridge, 2009). The colouring indicates brain areas with significant levels of blood flow. (B) In the normal brain, this brain network can be described in terms of the functional connectivity graphs. More strongly connected regions (indicated by heavier orange lines) are clustered near each other, while weakly correlated regions are placed further away with the line width proportional to the connection strength (Gao *et al.*, 2009). (C) Future challenges for DBS include how to best restore this default network in malignant disorders. We made a tentative start by using MEG to investigate how a DBS electrode implanted in the PVG/PAG region can help a wider network alleviate the suffering of chronic pain (Kringelbach *et al.*, 2007a). The 3D rendering shows the significant increases in activity in shades of orange, for example in regions such as the mid-anterior orbitofrontal cortex (white circle), while the other colours represent landmark brain structures: thalamus (green), cerebellum (blue) and brainstem (light blue). Abbreviations: IFG_L, IFG_R, left and right inferior frontal gyrus; LTC_L, LTC_R, left and right lateral temporal cortex; PCC, posterior cingulate cortex/retrosplenial; PL_L, PL_R, left and right parietal lobes; vmPFC, ventromedial prefrontal cortex.

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Abbreviations

BOLD, blood-oxygen level-dependent; DBS, deep brain stimulation; fMRI, functional magnetic resonance imaging; GP, globus pallidus; GPe, globus pallidus externa; GPi, globus pallidus interna; LFP, local field potential; MEG, magnetoencephalography; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PET, positron emission tomography; PPN, pedunculopontine nucleus; PVG/PAG, periventricular/periaqueductal grey; STN, subthalamic nucleus; Vim, ventral intermedius nucleus of the thalamus; VPL/VPM, ventral posterior lateral and medial nucleus of the thalamus.

References

Ackermans, L., Temel, Y., Cath, D., van der Linden, C., Bruggeman, R., Kleijer, M., Nederveen, P., Schruers, K., Colle, H., Tijssen, M.A. & Visser-Vandewalle, V. (2006) Deep brain stimulation in Tourette's syndrome: two targets? *Mov. Disord.*, **21**, 709–713.

Addis, D.R., Wong, A.T. & Schacter, D.L. (2007) Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*, **45**, 1363–1377.

Alessandro, S., Ceravolo, R., Brusa, L., Pierantozzi, M., Costa, A., Galati, S., Placidi, F., Romigi, A., Iani, C., Marzetti, F. & Peppe, A. (2010) Non-motor functions in parkinsonian patients implanted in the pedunculopontine nucleus: focus on sleep and cognitive domains. *J. Neurol. Sci.*, **289**, 44–48.

Alexander, G.E., DeLong, M.R. & Strick, P.L. (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.*, **9**, 357–381.

Anderson, M.E., Postupna, N. & Ruffo, M. (2003) Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. *J. Neurophysiol.*, **89**, 1150–1160.

Andy, O.J. & Jurko, F. (1987) Thalamic stimulation effects on reactive depression. *Appl. Neurophysiol.*, **50**, 324–329.

Aziz, T.Z., Peggs, D., Sambrook, M.A. & Crossman, A.R. (1991) Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. *Mov. Disord.*, **6**, 288–292.

Aziz, T.Z., Davies, L., Stein, J. & France, S. (1998) The role of descending basal ganglia connections to the brain stem in parkinsonian akinesia. *Br. J. Neurosurg.*, **12**, 245–249.

Ballanger, B., Jahanshahi, M., Broussolle, E. & Thobois, S. (2009a) PET functional imaging of deep brain stimulation in movement disorders and psychiatry. *J. Cereb. Blood Flow Metab.*, **29**, 1743–1754.

Ballanger, B., Lozano, A.M., Moro, E., van Eimeren, T., Hamani, C., Chen, R., Cilia, R., Houle, S., Poon, Y.Y., Lang, A.E. & Strafella, A.P. (2009b) Cerebral blood flow changes induced by pedunculopontine nucleus stimulation in patients with advanced Parkinson's disease: a [(15)O] H2O PET study. *Hum. Brain Mapp.*, **30**, 3901–3909.

Bejjani, B.P., Damier, P., Arnulf, I., Thivard, L., Bonnet, A.M., Dormont, D., Cornu, P., Pidoux, B., Samson, Y. & Agid, Y. (1999) Transient acute depression induced by high-frequency deep-brain stimulation. *N. Engl. J. Med.*, **340**, 1476–1480.

Benazzouz, A., Gross, C., Feger, J., Boraud, T. & Bioulac, B. (1993) Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. *Eur. J. Neurosci.*, **5**, 382–389.

Bergman, H., Wichmann, T. & DeLong, M.R. (1990) Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science (New York, NY)*, **249**, 1436–1438.

Beurrier, C., Bioulac, B., Audin, J. & Hammond, C. (2001) High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. *J. Neurophysiol.*, **85**, 1351–1356.

Bewernick, B.H., Hurlemann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., Axmacher, N., Lemke, M., Cooper-Mahkorn, D., Cohen, M.X., Brockmann, H., Lenartz, D., Sturm, V. & Schlaepfer, T.E. (2010) Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol. Psychiatry*, **67**, 110–116.

Biswal, B.B., Mennes, M., Zuo, X.N., Gohel, S., Kelly, C., Smith, S.M., Beckmann, C.F., Adelstein, J.S., Buckner, R.L., Colcombe, S., Dogonowski, A.M., Ernst, M., Fair, D., Hampson, M., Hoptman, M.J., Hyde, J.S., Kiviniemi, V.J., Kotter, R., Li, S.J., Lin, C.P., Lowe, M.J., Mackay, C., Madden, D.J., Madsen, K.H., Margulies, D.S., Mayberg, H.S., McMahon, K., Monk, C.S., Mostofsky, S.H., Nagel, B.J., Pekar, J.J., Peltier, S.J., Petersen, S.E., Riedl, V., Rombouts, S.A., Rypma, B., Schlaggar, B.L., Schmidt, S., Seidler, R.D., Siegle, G.J., Sorg, C., Teng, G.J., Veijola, J., Villringer, A., Walter, M., Wang, L., Weng, X.C., Whitfield-Gabrieli, S., Williamson, P., Windischberger, C., Zang, Y.F., Zhang, H.Y., Castellanos, F.X. & Milham, M.P. (2010) Toward discovery science of human brain function. *Proc. Natl. Acad. Sci. USA*, **107**, 4734–4739.

Boulet, S., Lacombe, E., Carcenac, C., Feuerstein, C., Sgambato-Faure, V., Poupard, A. & Savasta, M. (2006) Subthalamic stimulation-induced forelimb dyskinesias are linked to an increase in glutamate levels in the substantia nigra pars reticulata. *J. Neurosci.*, **26**, 10768–10776.

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P. & Di Lazzaro, V. (2001) Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J. Neurosci.*, **21**, 1033–1038.

Brown, P., Mazzone, P., Oliviero, A., Altibrandi, M.G., Pilato, F., Tonali, P.A. & Di Lazzaro, V. (2004) Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. *Exp. Neurol.*, **188**, 480–490.

Brudzynski, S.M., Houghton, P.E., Brownlee, R.D. & Mogenson, G.J. (1986) Involvement of neuronal cell bodies of the mesencephalic locomotor region in the initiation of locomotor activity of freely behaving rats. *Brain Res. Bull.*, **16**, 377–381.

Burns, R.S., Chiueh, C.C., Markey, S.P., Ebert, M.H., Jacobowitz, D.M. & Kopin, I.J. (1983) A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Proc. Natl. Acad. Sci. USA*, **80**, 4546–4550.

Clements, J.R. & Grant, S. (1990) Glutamate-like immunoreactivity in neurons of the laterodorsal tegmental and pedunculopontine nuclei in the rat. *Neurosci. Lett.*, **120**, 70–73.

Coffey, R.J. (2008) Deep brain stimulation devices: a brief technical history and review. *Artif. Organs*, **33**, 208–220.

Crossman, A.R., Mitchell, I.J. & Sambrook, M.A. (1985) Regional brain uptake of 2-deoxyglucose in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the macaque monkey. *Neuropharmacology*, **24**, 587–591.

Dostrovsky, J.O., Levy, R., Wu, J.P., Hutchison, W.D., Tasker, R.R. & Lozano, A.M. (2000) Microstimulation-induced inhibition of neuronal firing in human globus pallidus. *J. Neurophysiol.*, **84**, 570–574.

Durand, D.M. (2003) Electric field effects in hyperexcitable neural tissue: a review. *Radiat. Prot. Dosimetry*, **106**, 325–331.

Ford, B., Holmes, C.J., Mainville, L. & Jones, B.E. (1995) GABAergic neurons in the rat pontomesencephalic tegmentum: codistribution with cholinergic and other tegmental neurons projecting to the posterior lateral hypothalamus. *J. Comp. Neurol.*, **363**, 177–196.

Franzini, A., Ferroli, P., Leone, M. & Broggi, G. (2003) Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. *Neurosurgery*, **52**, 1095–1099. discussion 1099–1101.

Gao, W., Zhu, H., Giovanello, K.S., Smith, J.K., Shen, D., Gilmore, J.H. & Lin, W. (2009) Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. *Proc. Natl. Acad. Sci. USA*, **106**, 6790–6795.

Garcia, L., Audin, J., D'Alessandro, G., Bioulac, B. & Hammond, C. (2003) Dual effect of high-frequency stimulation on subthalamic neuron activity. *J. Neurosci.*, **23**, 8743–8751.

Garcia, L., D'Alessandro, G., Bioulac, B. & Hammond, C. (2005) High-frequency stimulation in Parkinson's disease: more or less? *Trends Neurosci.*, **28**, 209–216.

Garcia-Rill, E., Houser, C.R., Skinner, R.D., Smith, W. & Woodward, D.J. (1987) Locomotion-inducing sites in the vicinity of the pedunculopontine nucleus. *Brain Res. Bull.*, **18**, 731–738.

Georgi, J.C., Stippich, C., Tronnier, V.M. & Heiland, S. (2004) Active deep brain stimulation during MRI: a feasibility study. *Magn. Reson. Med.*, **51**, 380–388.

Giacobbe, P., Mayberg, H.S. & Lozano, A.M. (2009) Treatment resistant depression as a failure of brain homeostatic mechanisms: implications for deep brain stimulation. *Exp. Neurol.*, **219**, 44–52.

Gorwood, P. (2008) Neurobiological mechanisms of anhedonia. *Dialogues Clin. Neurosci.*, **10**, 291–299.

Gradinaru, V., Mogri, M., Thompson, K.R., Henderson, J.M. & Deisseroth, K. (2009) Optical deconstruction of parkinsonian neural circuitry. *Science (New York, NY)*, doi: 10.1126/science.1167093.

Green, A.L., Wang, S., Stein, J.F., Pereira, E.A., Kringelbach, M.L., Liu, X., Brittain, J.S. & Aziz, T.Z. (2009) Neural signatures in patients with neuropathic pain. *Neurology*, **72**, 569–571.

Grover, P.J., Pereira, E.A.C., Green, A.L., Brittain, J.-S., Owen, S.L.F., Schweder, P., Kringelbach, M.L., Davies, P.T. & Aziz, T.Z. (2009) Deep brain stimulation for cluster headache. *J. Clin. Neurosci.*, **16**, 861–866.

Gusnard, D.A. & Raichle, M.E. (2001) Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.*, **2**, 685–694.

Hammond, C., Bergman, H. & Brown, P. (2007) Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci.*, **30**, 357–364.

Hansen, P.C., Kringelbach, M.L. & Salmelin, R. (2010). *MEG. An Introduction to Methods*. Oxford University Press, Oxford.

Hashimoto, T., Elder, C.M., Okun, M.S., Patrick, S.K. & Vitek, J.L. (2003) Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J. Neurosci.*, **23**, 1916–1923.

Hershey, T., Revilla, F.J., Wernle, A.R., McGee-Minnich, L., Antenor, J.V., Videen, T.O., Dowling, J.L., Mink, J.W. & Perlmutter, J.S. (2003) Cortical and subcortical blood flow effects of subthalamic nucleus stimulation in PD. *Neurology*, **61**, 816–821.

Hillebrand, A. & Barnes, G.R. (2002) A quantitative assessment of the sensitivity of whole-head MEG to activity in the adult human cortex. *Neuroimage*, **16**, 638–650.

Holsheimer, J., Demeulemeester, H., Nuttin, B. & de Sutter, P. (2000) Identification of the target neuronal elements in electrical deep brain stimulation. *Eur. J. Neurosci.*, **12**, 4573–4577.

Hosobuchi, Y., Adams, J.E. & Rutkin, B. (1973) Chronic thalamic stimulation for the control of facial anesthesia dolorosa. *Arch. Neurol.*, **29**, 158–161.

Hosobuchi, Y., Adams, J.E. & Linchitz, R. (1977) Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone. *Science (New York, NY)*, **197**, 183–186.

Jenkinson, N., Nandi, D., Miall, R.C., Stein, J.F. & Aziz, T.Z. (2004) Pedunculopontine nucleus stimulation improves akinesia in a Parkinsonian monkey. *Neuroreport*, **15**, 2621–2624.

Jenkinson, N., Nandi, D., Muthusamy, K., Ray, N.J., Gregory, R., Stein, J.F. & Aziz, T.Z. (2009) Anatomy, physiology, and pathophysiology of the pedunculopontine nucleus. *Mov. Disord.*, **24**, 319–328.

Jimenez, F., Velasco, F., Salin-Pascual, R., Hernandez, J.A., Velasco, M., Criales, J.L. & Nicolini, H. (2005) A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *Neurosurgery*, **57**, 585–593. discussion 585–593.

Kita, H., Tachibana, Y., Nambu, A. & Chiken, S. (2005) Balance of monosynaptic excitatory and disynaptic inhibitory responses of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey. *J. Neurosci.*, **25**, 8611–8619.

Kojima, J., Yamaji, Y., Matsumura, M., Nambu, A., Inase, M., Tokuno, H., Takada, M. & Imai, H. (1997) Excitotoxic lesions of the pedunculopontine tegmental nucleus produce contralateral hemiparkinsonism in the monkey. *Neurosci. Lett.*, **226**, 111–114.

Kopell, B.H. & Greenberg, B.D. (2008) Anatomy and physiology of the basal ganglia: implications for DBS in psychiatry. *Neurosci. Biobehav. Rev.*, **32**, 408–422.

Kringelbach, M.L. (2005) The orbitofrontal cortex: linking reward to hedonic experience. *Nat. Rev. Neurosci.*, **6**, 691–702.

Kringelbach, M.L. & Aziz, T.Z. (2009) Deep brain stimulation: avoiding the errors of psychosurgery. *JAMA*, **301**, 1705–1707.

Kringelbach, M.L. & Berridge, K.C. (2009) Towards a functional neuroanatomy of pleasure and happiness. *Trends Cogn. Sci.*, **13**, 479–487.

Kringelbach, M.L., Jenkinson, N., Green, A., Hansen, P.C., Cornelissen, P.L., Holliday, I.E., Stein, J. & Aziz, T. (2006) Deep brain stimulation and chronic pain mapped with MEG. *Soc. Neurosci.*, **782.1**.

Kringelbach, M.L., Jenkinson, N., Green, A.L., Owen, S.L.F., Hansen, P.C., Cornelissen, P.L., Holliday, I.E., Stein, J. & Aziz, T.Z. (2007a) Deep brain stimulation for chronic pain investigated with magnetoencephalography. *Neuroreport*, **18**, 223–228.

Kringelbach, M.L., Jenkinson, N., Owen, S.L.F. & Aziz, T.Z. (2007b) Translational principles of deep brain stimulation. *Nat. Rev. Neurosci.*, **8**, 623–635.

Kringelbach, M.L., Owen, S.L.F. & Aziz, T.Z. (2007c) Deep brain stimulation. *Future Neurol.*, **2**, 633–646.

Kringelbach, M.L., Pereira, E.A.C., Green, A.L., Owen, S.L.F. & Aziz, T.Z. (2009) Deep brain stimulation for chronic pain. *J. Pain. Manag.*, **3**, 301–314.

Kuncel, A.M. & Grill, W.M. (2004) Selection of stimulus parameters for deep brain stimulation. *Clin. Neurophysiol.*, **115**, 2431–2441.

Langston, J.W., Ballard, P., Tetrud, J.W. & Irwin, I. (1983) Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science (New York, NY)*, **219**, 979–980.

Lauritzen, M. (2005) Reading vascular changes in brain imaging: is dendritic calcium the key? *Nat. Rev. Neurosci.*, **6**, 77–85.

Leblois, A., Boraud, T., Meissner, W., Bergman, H. & Hansel, D. (2006) Competition between feedback loops underlies normal and pathological dynamics in the basal ganglia. *J. Neurosci.*, **26**, 3567–3583.

Leblois, A., Meissner, W., Bioulac, B., Gross, C.E., Hansel, D. & Boraud, T. (2007) Late emergence of synchronized oscillatory activity in the pallidum during progressive Parkinsonism. *Eur. J. Neurosci.*, **26**, 1701–1713.

Lee, K.H., Blaha, C.D., Garris, P.A., Mohseni, P., Horne, A.E., Bennet, K.E., Agnesi, F., Bledsoe, J.M., Lester, D.B., Kimble, C., Min, H.K., Kim, Y.B. & Cho, Z.H. (2009) Evolution of Deep Brain Stimulation: Human Electrometer and Smart Devices Supporting the Next Generation of Therapy. *Neuromodulation*, **12**, 85–103.

Leone, M., Franzini, A., Broggi, G., May, A. & Bussone, G. (2004) Long-term follow-up of bilateral hypothalamic stimulation for intractable cluster headache. *Brain*, **127**, 2259–2264.

Li, S., Arbuthnott, G.W., Jutras, M.J., Goldberg, J.A. & Jaeger, D. (2007) Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. *J. Neurophysiol.*, **98**, 3525–3537.

Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Le Bas, J.F., Broussolle, E., Perret, J.E. & Benabid, A.L. (1995) Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet*, **345**, 91–95.

Litvak, V., Eusebio, A., Jha, A., Oostenveld, R., Barnes, G.R., Penny, W.D., Zrinzo, L., Hariz, M.I., Limousin, P., Friston, K.J. & Brown, P. (2010) Optimized beamforming for simultaneous MEG and intracranial local field potential recordings in deep brain stimulation patients. *Neuroimage*, **50**, 1578–1588.

Liu, Y., Postupna, N., Falkenberg, J. & Anderson, M.E. (2008) High frequency deep brain stimulation: what are the therapeutic mechanisms? *Neurosci. Biobehav. Rev.*, **32**, 343–351.

Logothetis, N.K. & Wandell, B.A. (2004) Interpreting the BOLD signal. *Annu. Rev. Physiol.*, **66**, 735–769.

Lou, H.C., Kjaer, T.W., Friberg, L., Wildschiodtz, G., Holm, S. & Nowak, M. (1999) A 15O-H2O PET study of meditation and the resting state of normal consciousness. *Hum. Brain Mapp.*, **7**, 98–105.

Mallet, N., Pogosyan, A., Sharott, A., Csicsvari, J., Bolam, J.P., Brown, P. & Magill, P.J. (2008) Disrupted dopamine transmission and the emergence of exaggerated beta oscillations in subthalamic nucleus and cerebral cortex. *J. Neurosci.*, **28**, 4795–4806.

May, A., Leone, M., Boecker, H., Sprenger, T., Juergens, T., Bussone, G. & Tolle, T.R. (2006) Hypothalamic deep brain stimulation in positron emission tomography. *J. Neurosci.*, **26**, 3589–3593.

Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwalb, J.M. & Kennedy, S.H. (2005) Deep brain stimulation for treatment-resistant depression. *Neuron*, **45**, 651–660.

Mazars, G., Roge, R. & Mazars, Y. (1960) [Results of the stimulation of the spinothalamic fasciculus and their bearing on the physiopathology of pain.]. *Rev. Prat.*, **103**, 136–138.

Mazars, G., Merienne, L. & Ciolocca, C. (1973) [Intermittent analgesic thalamic stimulation. Preliminary note]. *Rev. Neurol. (Paris)*, **128**, 273–279.

Mazzone, P., Lozano, A.M., Stanzione, P., Galati, S., Scanati, E., Peppe, A. & Stefani, A. (2005) Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease. *Neuroreport*, **16**, 1877–1881.

McIntyre, C.C. & Hahn, P.J. (2010) Network perspectives on the mechanisms of deep brain stimulation. *Neurobiol. Dis.*, **38**, 329–337.

McIntyre, C.C., Grill, W.M., Sherman, D.L. & Thakor, N.V. (2004a) Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. *J. Neurophysiol.*, **91**, 1457–1469.

McIntyre, C.C., Savasta, M., Kerkerian-Le Goff, L. & Vitek, J.L. (2004b) Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin. Neurophysiol.*, **115**, 1239–1248.

Mena-Segovia, J., Bolam, J.P. & Magill, P.J. (2004) Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? *Trends Neurosci.*, **27**, 585–588.

Mena-Segovia, J., Sims, H.M., Magill, P.J. & Bolam, J.P. (2008) Cholinergic brainstem neurons modulate cortical gamma activity during slow oscillations. *J. Physiol.*, **586**, 2947–2960.

Mena-Segovia, J., Micklem, B.R., Nair-Roberts, R.G., Ungless, M.A. & Bolam, J.P. (2009) GABAergic neuron distribution in the pedunculopontine nucleus defines functional subterritories. *J. Comp. Neurol.*, **515**, 397–408.
Mesulam, M.M., Geula, C., Bothwell, M.A. & Hersh, L.B. (1989) Human reticular formation: cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei and some cytochemical comparisons to forebrain cholinergic neurons. *J. Comp. Neurol.*, **283**, 611–633.
Miocinovic, S., Parent, M., Butson, C.R., Hahn, P.J., Russo, G.S., Vitek, J.L. & McIntyre, C.C. (2006) Computational analysis of subthalamic nucleus and lenticular fasciculus activation during therapeutic deep brain stimulation. *J. Neurophysiol.*, **96**, 1569–1580.
Miocinovic, S., Zhang, J., Xu, W., Russo, G.S., Vitek, J.L. & McIntyre, C.C. (2007) Stereotactic neurosurgical planning, recording, and visualization for deep brain stimulation in non-human primates. *J. Neurosci. Methods*, **162**, 32–41.
Miocinovic, S., Lempka, S.F., Russo, G.S., Maks, C.B., Butson, C.R., Sakaie, K.E., Vitek, J.L. & McIntyre, C.C. (2009) Experimental and theoretical characterization of the voltage distribution generated by deep brain stimulation. *Exp. Neurol.*, **216**, 166–176.
Mogenson, G.J. & Wu, M. (1988) Differential effects on locomotor activity of injections of procaine into mediodorsal thalamus and pedunculopontine nucleus. *Brain Res. Bull.*, **20**, 241–246.
Montgomery, E.B. Jr & Baker, K.B. (2000) Mechanisms of deep brain stimulation and future technical developments. *Neurol. Res.*, **22**, 259–266.
Montgomery, E.B. Jr & Gale, J.T. (2008) Mechanisms of action of deep brain stimulation(DBS). *Neurosci. Biobehav. Rev.*, **32**, 388–407.
Munro-Davies, L., Winter, J., Aziz, T.Z. & Stein, J. (2001) Kainate acid lesions of the pedunculopontine region in the normal behaving primate. *Mov. Disord.*, **16**, 150–151.
Nandi, D., Aziz, T.Z., Giladi, N., Winter, J. & Stein, J.F. (2002a) Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus. *Brain*, **125**, 2418–2430.
Nandi, D., Liu, X., Winter, J.L., Aziz, T.Z. & Stein, J.F. (2002b) Deep brain stimulation of the pedunculopontine region in the normal non-human primate. *J. Clin. Neurosci.*, **9**, 170–174.
Nowak, L.G. & Bullier, J. (1998a) Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. I. Evidence from chronaxie measurements. *Exp. Brain Res.*, **118**, 477–488.
Nowak, L.G. & Bullier, J. (1998b) Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. II. Evidence from selective inactivation of cell bodies and axon initial segments. *Exp. Brain Res.*, **118**, 489–500.
Nuttin, B.J., Gabriels, L.A., Cosyns, P.R., Meyerson, B.A., Andreewitch, S., Sunaert, S.G., Maes, A.F., Dupont, P.J., Gybels, J.M., Gielen, F. & Demeulemeester, H.G. (2003) Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery*, **52**, 1263–1272.
Pahwa, R., Wilkinson, S.B., Overman, J. & Lyons, K.E. (2005) Preoperative clinical predictors of response to bilateral subthalamic stimulation in patients with Parkinson's disease. *Stereotact. Funct. Neurosurg.*, **83**, 80–83.
Perlmutter, J.S. & Mink, J.W. (2006) Deep brain stimulation. *Annu. Rev. Neurosci.*, **29**, 229–257.
Perlmutter, J.S., Mink, J.W., Bastian, A.J., Zackowski, K., Hershey, T., Miyawaki, E., Koller, W. & Videen, T.O. (2002) Blood flow responses to deep brain stimulation of thalamus. *Neurology*, **58**, 1388–1394.
Plaha, P. & Gill, S.G. (2005) Bilateral deep brain stimulation of the pedunculopontine nucleus for idiopathic Parkinson's disease. *Neuroreport*, **16**, 1883–1887.
Pool, J.L., Clark, W.D., Hudson, P. & Lombardo, M. (1956). Steroid hormonal response to stimulation of electrodes implanted in the subfrontal parts of the brain. In Fields, W.S., Guillemin, R. & Carton, C.A. (Eds), *Hypothalamic-Hypophysial Interrelationships*. Charles C. Thomas Publisher, Springfield, IL, pp. 114–124.
Pralong, E., Debatisse, D., Maeder, M., Vingerhoets, F., Ghika, J. & Villemure, J.G. (2003) Effect of deep brain stimulation of GPI on neuronal activity of the thalamic nucleus ventralis oralis in a dystonic patient. *Neurophysiol. Clin.*, **33**, 169–173.
Ranck, J.B. Jr (1975) Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res.*, **98**, 417–440.
Ray, N.J., Kringelbach, M.L., Jenkinson, N., Owen, S.L.F., Davies, P., Wang, S., De Pennington, N., Hansen, P.C., Stein, J. & Aziz, T.Z. (2007) Using magnetoencephalography to investigate deep brain stimulation for cluster headache. *Biomed. Imaging Interv. J.*, **3**, e25.
Richardson, D.E. & Akil, H. (1977a) Long term results of periventricular gray self-stimulation. *Neurosurgery*, **1**, 199–202.
Richardson, D.E. & Akil, H. (1977b) Pain reduction by electrical brain stimulation in man. Part 1: acute administration in periaqueductal and periventricular sites. *J. Neurosurg.*, **47**, 178–183.
Richardson, D.E. & Akil, H. (1977c) Pain reduction by electrical brain stimulation in man. Part 2: chronic self-administration in the periventricular gray matter. *J. Neurosurg.*, **47**, 184–194.
Rolland, A.S., Tande, D., Herrero, M.T., Luquin, M.R., Vazquez-Claverie, M., Karachi, C., Hirsch, E.C. & Francois, C. (2009) Evidence for a dopaminergic innervation of the pedunculopontine nucleus in monkeys, and its drastic reduction after MPTP intoxication. *J. Neurochem.*, **110**, 1321–1329.
Rye, D.B., Saper, C.B., Lee, H.J. & Wainer, B.H. (1987) Pedunculopontine tegmental nucleus of the rat: cytoarchitecture, cytochemistry, and some extrapyramidal connections of the mesopontine tegmentum. *J. Comp. Neurol.*, **259**, 483–528.
Sachdev, P.S. & Chen, X.H. (2009) Neurosurgical treatment of mood disorders: traditional psychosurgery and the advent of deep brain stimulation. *Curr. Opin. Psychiatry*, **22**, 25–31.
Sakatani, K., Katayama, Y., Yamamoto, T. & Suzuki, S. (1999) Changes in cerebral blood oxygenation of the frontal lobe induced by direct electrical stimulation of thalamus and globus pallidus: a near infrared spectroscopy study. *J. Neurol. Neurosurg. Psychiatry*, **67**, 769–773.
Schiff, N.D., Giacino, J.T. & Fins, J.J. (2009) Deep brain stimulation, neuroethics, and the minimally conscious state. Moving beyond proof of principle. *Arch. Neurol.*, **66**, 697–702.
Schlaepfer, T.E., Cohen, M.X., Frick, C., Kosel, M., Brodesser, D., Axmacher, N., Joe, A.Y., Kreft, M., Lenartz, D. & Sturm, V. (2008) Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology*, **33**, 368–377.
Schnitzler, A. & Gross, J. (2005) Normal and pathological oscillatory communication in the brain. *Nat. Rev. Neurosci.*, **6**, 285–296.
Stefani, A., Lozano, A.M., Peppe, A., Stanzione, P., Galati, S., Tropepi, D., Pierantozzi, M., Brusa, L., Scarnati, E. & Mazzone, P. (2007) Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain*, **130**, 1596–1607.
Stefani, A., Pierantozzi, M., Ceravolo, R., Brusa, L., Galati, S. & Stanzione, P. (2010) Deep brain stimulation of pedunculopontine tegmental nucleus (PPTg) promotes cognitive and metabolic changes: a target-specific effect or response to a low-frequency pattern of stimulation? *Clin. EEG. Neurosci.*, **41**, 82–86.
Stefurak, T., Mikulis, D., Mayberg, H., Lang, A.E., Hevenor, S., Pahapill, P., Saint-Cyr, J. & Lozano, A. (2003) Deep brain stimulation for Parkinson's disease dissociates mood and motor circuits: a functional MRI case study. *Mov. Disord.*, **18**, 1508–1516.
Temel, Y., Kessels, A., Tan, S., Topdag, A., Boon, P. & Visser-Vandewalle, V. (2006) Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. *Parkinsonism Relat. Disord.*, **12**, 265–272.
Urbano, F.J., Leznik, E. & Llinas, R.R. (2002) Cortical activation patterns evoked by afferent axons stimuli at different frequencies: an in vitro voltage sensitive dye imaging study. *Thalamus Relat. Syst.*, **1**, 371–378.
Visser-Vandewalle, V., Temel, Y., Boon, P., Vreeling, F., Colle, H., Hoogland, G., Groenewegen, H.J. & van der Linden, C. (2003) Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette syndrome. Report of three cases. *J. Neurosurg.*, **99**, 1094–1100.
Vitek, J.L. (2002) Mechanisms of deep brain stimulation: excitation or inhibition. *Mov. Disord.*, **17**, S69–S72.
Volkmann, J., Herzog, J., Kopper, F. & Deuschl, G. (2002) Introduction to the programming of deep brain stimulators. *Mov. Disord.*, **17**, S181–S187.
Voon, V., Moro, E., Saint-Cyr, J.A., Lozano, A.M. & Lang, A.E. (2005) Psychiatric symptoms following surgery for Parkinson's disease with an emphasis on subthalamic stimulation. *Adv. Neurol.*, **96**, 130–147.
Weaver, F.M., Follett, K., Stern, M., Hur, K., Harris, C., Marks, W.J. Jr, Rothlind, J., Sagher, O., Reda, D., Moy, C.S., Pahwa, R., Burchiel, K., Hogarth, P., Lai, E.C., Duda, J.E., Holloway, K., Samii, A., Horn, S., Bronstein, J., Stoner, G., Heemskerk, J. & Huang, G.D. (2009) Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*, **301**, 63–73.
Windels, F., Bruet, N., Poupard, A., Urbain, N., Chouvet, G., Feuerstein, C. & Savasta, M. (2000) Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. *Eur. J. Neurosci.*, **12**, 4141–4146.