The autonomic effects of deep brain stimulation—a therapeutic opportunity

Jonathan A. Hyam, Morten L. Kringelbach, Peter A. Silburn, Tipu Z. Aziz and Alexander L. Green

Abstract | Deep brain stimulation (DBS) is an expanding field in neurosurgery and has already provided important insights into the fundamental mechanisms underlying brain function. One of the most exciting emerging applications of DBS is modulation of blood pressure, respiration and micturition through its effects on the autonomic nervous system. DBS stimulation at various sites in the central autonomic network produces rapid changes in the functioning of specific organs and physiological systems that are distinct from its therapeutic effects on central nervous motor and sensory systems. For example, DBS modulates several parameters of cardiovascular function, including heart rate, blood pressure, heart rate variability, baroreceptor sensitivity and blood pressure variability. The beneficial effects of DBS also extend to improvements in lung function. This article includes an overview of the anatomy of the central autonomic network, which consists of autonomic nervous system components in the cortex, diencephalon and brainstem that project to the spinal cord or cranial nerves. The effects of DBS on physiological functioning (particularly of the cardiovascular and respiratory systems) are discussed, and the potential for these findings to be translated into therapies for patients with autonomic diseases is examined.

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Introduction

Neurostimulation was first used in ancient Rome after the discovery that treading on a torpedo fish (electric ray) could ameliorate gout pain.[1] This insight led to the development of sophisticated electrical stimulation therapies that are applied to numerous sites around the body to treat a variety of disorders. Deep brain stimulation (DBS) is now an established therapy for movement disorders, such as Parkinson disease (PD) and tremor,[2–6] and has been used to treat a variety of chronic pain syndromes[4,7,8] and psychiatric disorders.[9,10] Some of these disease states are associated with dysautonomias, a group of conditions in which changes in the activity or function of the autonomic nervous system adversely affect health.[11] Dysautonomias can result either from a primary abnormality of the autonomic nervous system or from its dysregulation, and can be seen in isolation or as manifestations of other disease states, such as PD.[12] Awareness of the role of the autonomic nervous system in diseases throughout the body is increasing and dysautonomia has been implicated even in common conditions, such as asthma.[13] As a result, the effects of DBS on autonomic nervous system functioning are attracting increased interest. In particular, improved understanding of the role of the autonomic nervous system in modulation of cardiovascular performance, respiration and micturition could make treatment of dysfunctions of these processes one of the most exciting and novel applications of DBS.

In this Review, we describe the anatomy of the CNS components that make up the central autonomic network (CAN), which is part of the autonomic nervous system. These components are derived from every level of the brain, from cortex to diencephalon and brainstem, and they project to the spinal cord or connect with cranial nerves. We describe the effects of DBS in this network on physiological functions, particularly of the cardiovascular and respiratory systems, and present evidence supporting a beneficial effect of DBS on the clinical manifestations of dysautonomia.

The effects of DBS on neural subtrates

In disease states, one or more intracerebral sites might be identified as having a beneficial response to DBS, which involves chronic administration of extracellular pulses of direct current at frequencies of 20–200 Hz.[14] This treatment is thought to stimulate local nerve fibres and modulate large oscillatory brain networks (Figure 1).[15,16] DBS might also restore the activity of brain networks to resting-state levels.[17] Low-frequency stimulation has been suggested to provide an excitatory drive, whereas high-frequency stimulation (>100 Hz) is thought to have an inhibitory effect, as it produces the same clinical effect as a destructive lesion.[14] This model is very simplified and the reality is likely to be much more complex; for example, neurophysiological data suggest that high-frequency stimulation of some regions, such as the subthalamic

Competing interests
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Key points

- Discrete structures within all levels of the CNS, from the cortex to the medulla, comprise the central autonomic network
- The central autonomic network coordinates information from the CNS and PNS, which enables it to mediate autonomic responses rapidly
- Deep brain stimulation (DBS) produces autonomic sequelae in some patients during the electrode implantation procedure, and at subsequent testing
- DBS of the posterior hypothalamus, subthalamic nucleus (STN) and periaqueductal grey (PAG) can cause changes in cardiovascular indices at rest and during postural challenge
- In patients with chronic pain or movement disorders, lung function improvements seemingly unrelated to amelioration of the underlying syndrome can occur with DBS of the STN or PAG
- DBS could in the future provide a therapeutic option for patients with dysautonomias that affect a variety of body systems

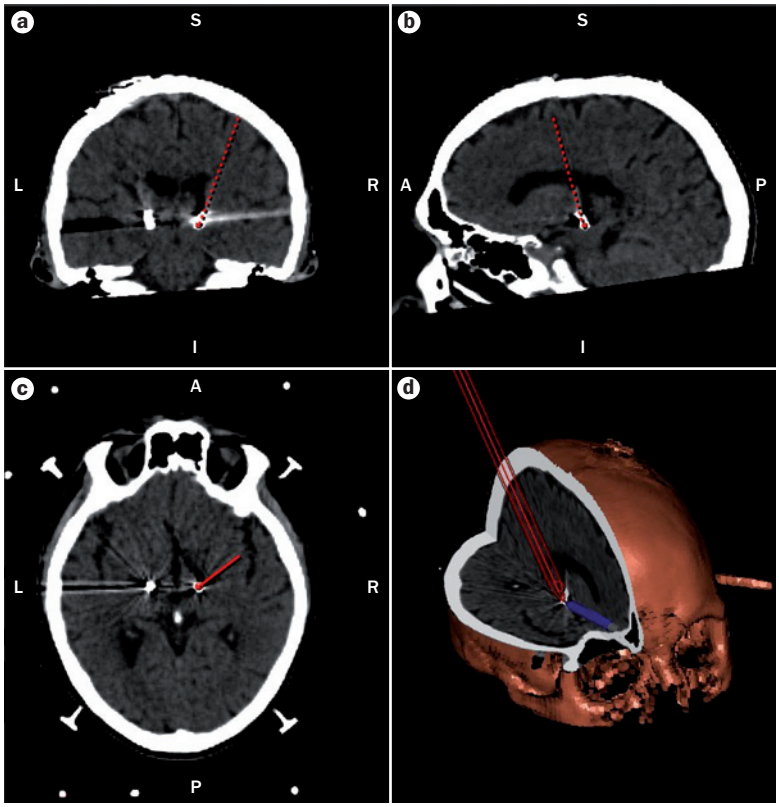

Figure 1 | Stereotactic mapping of the brain of a patient undergoing deep brain stimulation. The images show the positioning of macroelectrodes implanted bilaterally in the subthalamic nucleus. **a** | Coronal CT view. **b** | Sagittal CT view. **c** | Axial CT view. **d** | Reconstructed 3D image, confirming location of the electrodes in the subthalamic nucleus. Red lines in all panels depict trajectory of electrode. Blue line points to tip of right electrode within subthalamic nucleus. Panels a–c were constructed by fusion of preoperative MRI and postoperative CT images, and panel d is a reconstructed 3D image. All images are from the same patient. Abbreviations: A, anterior; I, inferior; L, left; P, posterior; R, right; S, superior.

nucleus (STN), might in fact have an excitatory effect.[18,19] Therefore, the exact mechanism of action of DBS remains unclear, and is the subject of ongoing investigation.

Our understanding of the mechanisms by which DBS may modulate autonomic function has come from neuroimaging studies and direct studies of DBS in animals and humans.[19–27] These studies have also furthered our knowledge of the anatomy of the CNS components that comprise the autonomic network, described below, including identification of a so-called central command feedforward circuit. This circuit includes components within the CAN, such as the periaqueductal grey (PAG), that can modulate cardiovascular and respiratory responses.[28–30]

The central autonomic network

The autonomic nervous system is a complex network that is not only based on feedback loops, but also involves a series of important processing steps within the brain, whereby the efferent outflow is modulated. This sequence requires integration of ascending information from the afferent limb of the autonomic nervous system and other higher neural circuits, such as reticular and forebrain attentional, emotional and motivational systems, and sleep-wake cycle pathways, all of which depict the individual's current environmental and situational context, so that an appropriate response can be effected via sympathetic and parasympathetic outflows.[31] Through these numerous connections, the CAN—the intracranial portion of the autonomic nervous system—influences and modulates the function of organs and physiological systems throughout the body (Box 1).[31–34]

Afferent pathways

Ascending information from peripheral sites is coordinated in the CAN and first received at the nucleus of the solitary tract (NTS), which is in the medulla oblongata. Neural transmission involves two pathways: in the first, visceral afferents from the thoracolumbar (sympathetic) and craniosacral (parasympathetic) levels enter the spinal cord and terminate at the NTS. Glossopharyngeal and vagus nerves also transmit information to the NTS from arterial baroreceptors in the aortic arch and carotid sinus, cardiac baroreceptors in the ventricular and atrial walls, and arterial chemoreceptors in the aortic and carotid bodies.[35] The second pathway begins at the area postrema, a circumventricular organ that has an incomplete blood–brain barrier and is located on the floor of the fourth ventricle. This region is increasingly recognized to be important in cardiovascular regulation, as well as emesis.[35] Plasma electrolyte, humoral and cerebrospinal fluid chemical information from the circulation and the fourth ventricle arrives at the area postrema and is transmitted via a direct neural connection to the NTS.[32] This information is then relayed along nerve tracts from the NTS to multiple rostral sites that are part of the CAN, including the Kölliker–Fuse nucleus, hypothalamus, insula and amygdala.[31]

Efferent pathways

The NTS also has many complex and reciprocal connections to other CAN components (Box 1).[31] The terminal pathways of the CAN project from the medulla to the intermediolateral spinal cord or vagus nerve. The NTS is, therefore, a crucial junction in both afferent and efferent limbs of the CAN; this nucleus is also the point at which either sympathetic or parasympathetic drive is selected. The NTS projects to the rostroventrolateral medulla, a site that is recognized to be a key regulator of arterial

blood pressure and a component of the cardiovascular sympathetic outflow, which sends a number of large projections to the sympathetic intermediolateral spinal cord.[36,37] Located within the rostroventrolateral medulla are the neurons responsible for the tonic excitation of preganglionic vasomotor efferents, which are pivotal to several circuits, including the defence reaction and the somatosympathetic and baroreceptor reflexes.[31] Direct rostroventrolateral medulla stimulation produces elevations in sympathetic nerve activity and cardiovascular parameters (namely heart rate, blood pressure and catecholamine levels).[37] Parasympathetic outflow is mediated by projections from the NTS to the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve, which contain parasympathetic preganglionic neurons. These circuits then exit via the brainstem and are the main efferent sites in the medulla. In this way, the CAN orchestrates the balance between parasympathetic and sympathetic drive, which is a crucial determinant of end-organ functions, including heart rate.

Modulation of autonomic responses

The arterial baroreflex provides an insight into how the brainstem CAN mediates rapid, moment-to-moment changes that dynamically alter the balance between sympathetic and parasympathetic activity in response to changing cardiorespiratory demands. Default sympathetic resting activity results in a chronotropic, inotropic and vasoconstrictive tendency to the cardiovascular system. Baroreceptors in the carotid sinus and the aortic arch continuously transmit to the NTS as the arterial walls are stretched, via the glossopharyngeal and vagus nerves, respectively.[38] When arterial stretch is detected in the baroreceptors, the rostroventrolateral medulla is inhibited by the NTS, which at the same time excites the nucleus ambiguus and dorsal motor nucleus of the vagus nerve, which produces a reduction in sympathetic tone and an increase in vagal activity. The end result is a decrease in heart rate mediated by the sinoatrial node, in addition to vasodilatory and negative inotropic effects. As this medullary outflow is downstream from higher CAN centres, these cortical and subcortical structures can modulate these reflexes (and ultimately the end-organ behaviour) in response to contextual information from other networks, such as the limbic or arousal systems.

Central command

Central command is a top-down, feedforward mechanism whereby higher brain areas modulate cardiorespiratory responses immediately before and during exercise.[29,39,40] This pathway provides a mechanism for alteration of cardiorespiratory function, to achieve levels of tissue perfusion, oxygen intake and carbon dioxide output that are adequate for the expected degree of exercise to be undertaken. Immediately prior to and during exercise, therefore, cardiorespiratory variables such as heart rate, arterial blood pressure and respiratory rate are elevated above resting levels. This alteration is independent of actual motor activity and is seen in hypnotized individuals asked to imagine exercise; this mechanism might also underlie the phenomena of emotional syncope and 'white coat' hypertension.[26,30]

Box 1 | Components of the CAN

The CAN is composed of components from every neurodevelopmental level within the brain, from the cortex and diencephalon to the brainstem, which extend projections to the spinal cord or make connections with cranial nerves.

Afferent limb

Cerebral cortex
- Insula and amygdala

Diencephalon
- Thalamus, hypothalamus

Subcortical structures
- Kölliker–Fuse nucleus, parabrachial nucleus and A5-cell group in the pons
- Nucleus tractus solitarius in the medulla oblongata

Efferent limb

Cerebral cortex
- Anterior cingulate gyrus, amygdala, insula (often referred to as the visceral primary sensorimotor cortex)[105,106]

Diencephalon
- Lateral area of the hypothalamus

Subcortical structures
- Periventricular and periaqueductal grey of the midbrain*
- Locus coeruleus and parabrachial nuclei of the pons
- Medulla oblongata (specifically the nucleus tractus solitarius, nucleus ambiguus, dorsal motor nucleus of the vagus nerve and the rostroventrolateral medulla)[31,32,107]

*For the purposes of this article these two areas are considered together. Abbreviation: CAN, central autonomic network.

Functional MRI and PET studies have implicated the insula, medial prefrontal areas such as the anterior cingulate cortex, and the thalamus in this mechanism.[26,41–44] Electrical activity has also been directly measured in humans, using indwelling deep brain electrodes. These studies indicated that two subcortical sites were involved in this process, the STN in the diencephalon (a site that has important memory and learning functions, as well as limbic system and motor cortex connections), [45–48] and the PAG (Figure 2).[28] Changes in local electrical field potentials in the STN and PAG during the anticipation of exercise and during exercise performance increased in parallel with elevations in cardiorespiratory variables.[40] Thus, components within the CAN are responsible for driving end-organ performance, independently of activity within the organ itself. The CAN is, therefore, a tantalizing potential target for neuromodulation therapies, by virtue of its top-down connection with (and rapid effects on) key organ systems.

Therapeutic applications of DBS

Implantation of state-of-the-art neural prostheses, such as indwelling deep brain electrodes, has facilitated the study of deep brain sites in awake patients in resting states, and even under controlled experimental conditions. DBS using such electrodes is already approved for the treatment of movement disorders such as essential tremor, PD and dystonia, and has been reviewed elsewhere. [10,24] However, a wide range of inadvertent

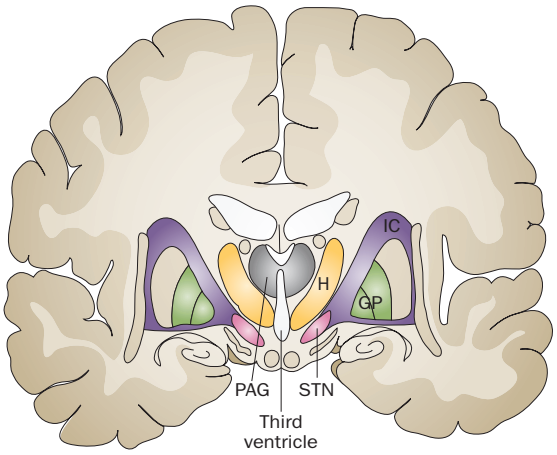

Figure 2 | Targets for DBS. Diagram showing the human brain in coronal section at the level of the midbrain and diencephalon; the PAG, hypothalamus and subthalamic nucleus are indicated. Despite the close proximity of these structures, they are the DBS targets for the treatment of diverse conditions, namely chronic pain, cluster headache, and movement disorders, respectively. Abbreviations: DBS, deep brain stimulation. GP, globus pallidus; H, hypothalamus; IC, internal capsule; PAG, periventricular–periaqueductal grey; STN, subthalamic nucleus.[107]

autonomic effects can be encountered in as many as 20% of patients during intraoperative testing of DBS and during postimplantation optimization of stimulation.[49] Adverse autonomic effects can usually be ameliorated by altering stimulation parameters or the configuration of active electrode contacts or, ultimately, by adjustment of the electrode position. In the future, therefore, this technique might be used to treat various diseases that have an autonomic component (Table 1).

Cardiovascular and respiratory modulation

In the past, progress in understanding how the brain modulates cardiovascular and respiratory function generally came from studies in animals. For example, the effect of orbitofrontal cortex stimulation on respiratory rate was demonstrated in rabbits, cats, dogs and monkeys as long ago as 1894,[50] and the potential for the midbrain to modulate blood pressure was described in the cat in 1935.[23] In the 20th century, the advent of neurosurgery as a subspecialty in its own right, allied with advances in anaesthesia and neuroimaging, has facilitated intraoperative investigation of these brain areas in humans. Intraoperative stimulation of cortical sites, such as the temporal lobes and anterior cingulate cortex, causes profound changes in cardiorespiratory function, and can even produce asystole.[51, 52]

DBS of the posterior hypothalamus

The hypothalamus (Figure 2) is pivotal to the integration of endocrine and autonomic responses in the maintenance of physiological homeostasis, and was historically known as the ergotropic area in view of its effects on sympathetic activity.[53,54] In a patient with PD in whom DBS electrodes were inadvertently placed close to the posterior hypothalamus, blood pressure and respiratory rate increased after activation of electrode stimulation.[55]

Local and central autonomic involvement is also well-documented in cluster headache. During an attack, ipsilateral symptoms (such as conjunctival injection, Horner syndrome and lacrimation) are observed in conjunction with intense pain and a concurrent increase in parasympathetic activity.[56] The hypothalamus is suggested as the source of this autonomic dysfunction, on the basis of its specific activation as observed in PET and functional MRI studies of cluster headache, its role within the CAN, and the regularity of daily attacks being in keeping with its function in maintenance of the circadian rhythm.[57]

DBS of the posterior hypothalamus is a novel treatment for refractory cluster headache.[58,59] In addition to the effects on the headache symptoms, the orthostatic sympathoexcitatory response was enhanced during head uptilt testing (HUTT) in patients with cluster headache who were receiving posterior hypothalamic stimulation via indwelling deep brain electrodes.[21] When the stimulation was turned off, HUTT resulted in a 3% fall in systolic blood pressure, whereas systolic blood pressure was maintained when the test was repeated during stimulation. Diastolic blood pressure and total peripheral resistance both increased significantly from 64 mmHg to 67 mmHg and 0.79 dyn s/cm^5 to 0.84 dyn s/cm^5, respectively (P <0.05 for HUTT on versus off DBS stimulation), which suggests that DBS affected the peripheral vascular system.

Heart rate variability (HRV) is a noninvasive index of autonomic activity that is widely employed in cardiovascular research and clinical practice,[60] whereby high-frequency changes in heart rate are attributed to fast vagal parasympathetic effects. In patients with cluster headache, HRV was found to change with hypothalamic stimulation (that is, the ratio of low-frequency:high-frequency HRV components increased), which suggests sympathetic activation mediated by DBS of the hypothalmus. The reverse HRV pattern was observed in patients with untreated cluster headache: during attacks, a significant reduction in low-frequency HRV values was observed, suggestive of autonomic nervous system dysfunction.[61] Electrocardiographic changes can also be seen in untreated patients during cluster headache; these changes include increases or decreases in heart rate and rhythm, with atrial fibrillation and heart block being reported during ambulatory Holter monitoring.[61,62] Putative mechanisms underlying these changes include trigeminal parasympathetic discharge producing vasodilatation, which compromises and inhibits the function of the traversing sympathetic fibres within the carotid canal.[56] Together, these studies provide important evidence that DBS of the posterior hypothalamus can improve autonomic function specifically during orthostatic challenge.

DBS of the subthalamic nucleus

The STN is situated in the diencephalon inferior to the thalamus and zona incerta (Figure 1) and is divided into associative, limbic and motor components.[18] Stimulation anteromedial or lateral to the STN has been implicated

in the production of various autonomic effects.[63] Lateral to the STN is the internal capsule (Figure 2), the anterior limb of which is a novel target of DBS in patients with obsessive–compulsive disorder.[64] Autonomic effects reported during DBS of the internal capsule anterior limb include sweating, increased respiratory rate, increased heart rate, cold and hot sensations, and involuntary emotions, such as fear and panic.[65,66] These effects were voltage-dependent and peaked at 6–8 V.[65,66]

Autonomic effects encountered during intraoperative testing of STN stimulation in patients with PD were predominantly of two types: subjective reports of dizziness, malaise, anxiety, and sensations of cold or warmth in the face or diffusely throughout the body; and objective findings of unilateral or bilateral excessive sweating, flushing, bilateral or unilateral midriasis, a mean increase in heart rate of 25 bpm, and a mean increase in systolic blood pressure of 20 mmHg.[49] These effects, which were both objective and subjective, showed no pattern of laterality and were voltage-dependent, occurring at a mean of 3.14 V. Notably, these autonomic effects were associated with stimulation of locations that provided the greatest improvement in motor symptoms, which suggests that the effects were being mediated by the portion of the STN that controls motor function, rather than by other local structures.[49]

Although the STN is an established target for DBS in patients with PD, this nucleus is not recognized to be part of the CAN. However, a number of studies involving DBS of this region have produced alterations in autonomic functioning.[27,67] In patients with PD treated with DBS of the STN, high-frequency (>100 Hz) stimulation during the implantation procedure produced mean increases of 5 bpm in heart rate and 5 mmHg in arterial blood pressure, but no such changes were observed in patients with PD undergoing DBS of the globus pallidus.[67] Manifestations of dysautonomia, including orthostatic hypotension and sudomotor disturbances, are common in patients with PD;[12] consequently, the prospect that DBS of the STN could improve autonomic function in addition to alleviating motor symptoms in these patients is attractive. Although two studies of HUTT in patients undergoing DBS of the STN reported no beneficial results,[68,69] a further study demonstrated an increase in heart rate, a reduction in blood flow to the skin, and maintenance of both arterial blood pressure and baroreceptor sensitivity, after 60° HUTT.[67] Further evidence that DBS of the STN might improve sudomotor function has been demonstrated in a study that used an autonomic symptom questionnaire and skin surface electrode recordings in 19 patients with PD.[70] In these patients, dyshidrosis manifestations were reduced by 67% on STN stimulation.

The mechanism by which DBS of the STN causes changes in autonomic function is not known; however, in our opinion, these effects might either be mediated via activation of the nonmotor functions of the STN, leading to limbic system activation, or result from indirect stimulation of components of the CAN that are in close proximity to the STN, such as the hypothalamus (Figure 2).[24] Indeed, the case report described above, in which STN electrodes inadvertently positioned close to the posterior hypothalamus resulted in autonomic modulation, provides some evidence for the latter hypothesis.[55] The increased frequencies and total energy delivery required for DBS of the STN to be clinically effective (compared with DBS in other brain regions, such as the PAG) might enable a wider spread of stimulation to affect a larger region of brain tissue.

Table 1 | Autonomic systems modulated by DBS

Autonomic system	DBS target	Conditions potentially amenable to DBS therapy
Cardiovascular	Subthalamic nucleus, posterior hypothalamus, periaqueductal grey	Hypertension, orthostatic hypotension
Respiratory	Subthalamic nucleus, periaqueductal grey	Asthma, chronic obstructive pulmonary disease, obstructive sleep apnoea
Sudomotor	Subthalamic nucleus	Dyshidrosis
Urinary	Subthalamic nucleus	Detrusor instability

Abbreviation: DBS, deep brain stimulation.

DBS of the periaqueductal grey

The PAG of the midbrain has been extensively investigated as a target of DBS, mainly as a treatment for pain syndromes.[7,8] The pain and autonomic nervous system pathways are intricately linked; however, the relationship is complex and has not yet been clearly defined. Intracranial areas important in both pain processing and autonomic function, including the NTS, PAG and locus coeruleus, show anatomical overlap.[71] The PAG seems to have a crucial role in the pain pathway and in integration of this pathway with afferent input from associated responses. The structure of the PAG is divided into four longitudinal columns, each of which is involved in different physiological responses.[72,73] A dynamic balance between facilitation and inhibition of nociception is orchestrated by a control network originating from the PAG, and is crucial for mediating successful survival behaviour such as protection and threat evasion. Owing to the multiple inputs received by the PAG from organs throughout the body and via the vagus nerve,[74,75] this region is ideally positioned to detect changes elsewhere in the body and to initiate the appropriate autonomic and behavioural responses.[74,75]

The PAG is instrumental in the 'flight or fight' reaction, an essential mechanism for promoting survival.[76] In the rat, this reaction results in increased heart rate and blood pressure, non-opioid-mediated analgesia, fear reactions,[77] and other autonomic responses, including pupillary and skeletal muscle activity changes, vocalization and micturition.[78] Conversely, if attack or escape are not possible, the 'coping' or 'passive' reaction manifests as decreased heart rate and blood pressure, opioid-mediated analgesia and freezing behaviour, as well as fear.[79,80]

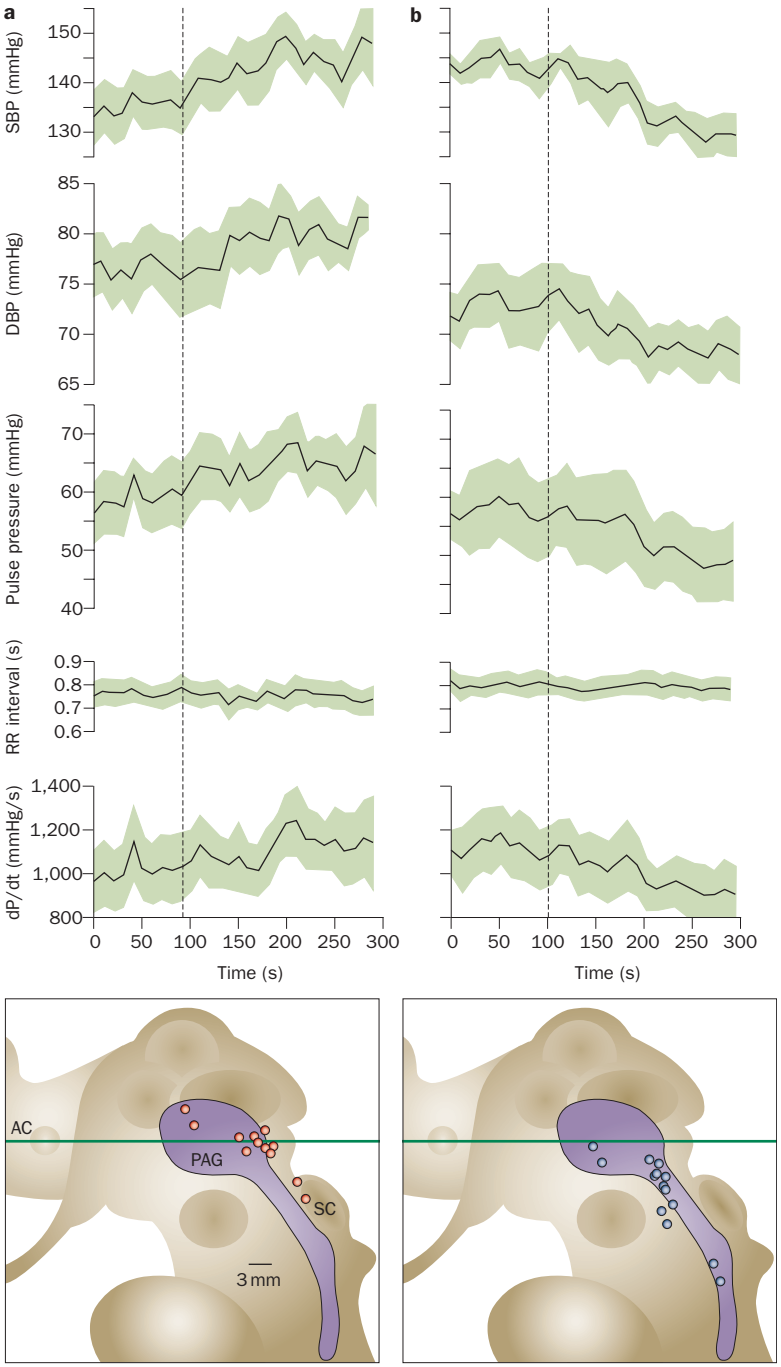

Figure 3 | The effect of PAG DBS on cardiovascular parameters. The schematics show sagittal sections of the brain through the PAG. The graphs show that alterations in cardiovascular parameters other than the RR interval occur after electrical stimulation activated at the 100 s start time point (black vertical lines). **a** | DBS of the dorsal PAG resulted in increases in cardiovascular parameters. Red dots indicate active electrode contact positions. **b** | DBS of the ventral PAG, by contrast, resulted in decreases in cardiovascular parameters. Blue dots indicate active electrode contact positions. Abbreviations: AC, anterior commissure; DBS, deep brain stimulation; DBP, diastolic blood pressure; dP/dt (blood–pressure waveform, a surrogate marker of cardiac contractility); PAG, periaqueductal grey; RR, respiratory rate; SBP, systolic blood pressure; SC, superior colliculus.

Electrical stimulation of the ventrolateral columns of the PAG in animals produces bradycardia, hypotension and freezing behaviour, whereas stimulation of the dorsolateral and dorsomedial columns of the PAG produces elevated heart rate and blood pressure.[72,81–84] In humans treated with DBS for chronic pain syndromes, the same phenomena were observed.[22] In patients at rest in a seated position, stimulation using dorsally located PAG electrodes produced an elevation of approximately 16 mmHg in systolic blood pressure, whereas stimulation using ventrally located PAG electrodes caused a decrease of approximately 14 mmHg in this parameter (Figure 3).[22] Intraoperative stimulation of the PAG results in systolic blood pressure changes that are associated with changes in HRV.[85] The absolute low-frequency and high-frequency HRV, as well as the ratio of low-frequency to high-frequency components, increased or decreased in parallel with the changes in systolic blood pressure. Although only the low-frequency component of HRV showed a significant correlation with systolic blood pressure, this association accounted for 70% of HRV variance .[85]

Stimulation of the PAG can also prevent the postural drop in blood pressure that occurs on moving from a sitting to a standing position.[86] This effect has been seen not only in patients with mild orthostatic intolerance, but also in one patient with clinical orthostatic hypotension, in whom systolic blood pressure fell by 15% from baseline (145–148 mmHg) on changing from a sitting to standing position without stimulation, compared with a change of only 0.1% on stimulation.[86] This study provided further insight into the mechanism by which PAG stimulation might cause blood pressure changes. Blood pressure is the product of cardiac output and peripheral vascular resistance, whereas cardiac output is the product of stroke volume and heart rate. Stroke volume is, in turn, determined by end-diastolic volume and cardiac contractility. In the patient with orthostatic hypotension, absolute heart rate did not differ significantly. During stimulation, the low-frequency component of HRV was maintained during standing from sitting, whereas without stimulation this parameter showed a significant decline (from 69.8 ms^2 to 7.0 ms^2.[83] Pulse pressure, which is a surrogate marker of peripheral vascular resistance, increased by 1.7% from a baseline of 71 mmHg on standing during stimulation, but fell by 10% when the stimulation was turned off. [86] Furthermore, the maximal gradient of each blood-pressure waveform (dP/dt, a surrogate marker of cardiac contractility) increased under both conditions but to a greater extent with stimulation (10%) than without (6%). Baroreceptor sensitivity increased during sitting with stimulation on; it falls during standing with both on and off states, but not to as great an extent as with stimulation on.[86] These data suggest that PAG stimulation exerts both central and peripheral cardiovascular effects.

Further investigations into the effects of PAG stimulation on the peripheral vascular tree and blood flow involved measurement of flow-mediated dilation by means of Doppler ultrasonography. In a single patient with chronic pain, PAG stimulation, compared with the stimulation switched off, produced a decrease in blood pressure, no change in heart rate, and a decrease in total peripheral resistance that occurred coincidently with

increases in brachial artery flow, consistent with vasodilation.[20] Further questions remain unanswered; for example, whether renal function, hormone secretion and circulating plasma volumes are altered on stimulation, and whether the same responses occur in patients without chronic pain syndromes. The available evidence suggests that PAG stimulation affects peripheral vascular resistance, which might, therefore, indirectly alter contractility by influencing end-diastolic volume. Alternatively, stimulation of the PAG might directly increase contractility. In contrast to its peripheral vascular effects, PAG stimulation does not seem to affect heart rate; thus, DBS of the PAG does not seem to alter blood pressure via a chronotropic mechanism.

Two case reports have documented long-term clinical data from PAG stimulation.[25,87] A sustained and statistically significant reduction in ambulatory blood pressure was observed 1 year after electrode implantation in a hypertensive patient undergoing PAG stimulation to treat facial pain. This individual had a mean diurnal blood pressure of 131/85 mmHg on stimulation, versus 144/96 mmHg with stimulation off. Moreover, DBS of the PAG remained efficacious for alleviating facial pain over the study period; treatment reduced the visual analogue pain score from 79% to 64%—a statistically significant result.[25] Another study found a strong positive correlation between blood pressure and scores on the McGill Pain Questionnaire after 1 year of DBS in the PAG.[88]

Since an important relationship exists between pain relief and changes in blood pressure, these observations raise the possibility that the observed cardiovascular effects of PAG stimulation might simply be a result of alleviating acute pain, and might not be reproducible in pain-free patients. However, a patient with refractory hypertension who was undergoing PAG stimulation to treat poststroke pain experienced persistent cardiovascular effects of DBS without sustained pain relief.[87] Although pain scores in this individual returned to preoperative levels within 4 months after electrode implantation, the reduction in blood pressure was maintained, and at 27 months blood pressure was significantly lower—by up to 33/13 mmHg—in on-stimulation than in off-stimulation periods.[87]

Modulation of respiratory function

The importance of the medulla oblongata in control of respiration has long been recognized,[89] and advances in noninvasive neuroimaging and functional neurosurgery have now made delineation of the relevant neurocircuitry possible.[52,24,90–92] Airway smooth-muscle contraction, glandular secretion, blood flow and microvascular permeability are modulated by the parasympathetic nervous system via airway-related vagal preganglionic neuron (AVPN) projections from the medulla that have synapses with vagal postganglionic neurons, which ultimately innervate the airways.[93] Tonic relaxation of airway smooth muscle is mediated by the sympathetic nervous system via circulating catecholamines.[13] Connections to AVPNs from multiple sites within the CAN, such as the amygdala, PAG, dorsal pons and medulla, were visualized via retrograde transneuronal labelling with pseudorabies virus in C8 spinal-cord-transected rats.[94,95] Haxhiu *et al.*[96] hypothesize that these sites maintain an inhibitory tone over the activity of AVPNs, thereby attenuating their cholinergic bronchoconstrictive effect.

Alteration of the respiratory rate by direct electrical stimulation of the anterior cingulate cortex was demonstrated during open brain surgery more than 50 years ago.[52] However, the effects of DBS on respiration are not limited to respiratory rate modulation. Among 20 patients with movement disorders or chronic pain syndromes who received DBS of the PAG or STN, the mean peak expiratory flow rate increased significantly, by 14%, during stimulation periods, compared with the off-stimulation state.[66] In 17 control patients with similar pathology who received DBS in regions not implicated in autonomic modulation, peak expiratory flow rate did not change, despite therapeutic benefits related to their pain or movement symptoms. In the movement-disorder group, the change in thoracic circumference associated with forced expiration was not correlated with increases in peak expiratory flow rate, which suggests that increased effort by skeletal muscle was not the main driver of the improvement in peak expiratory flow rate. Furthermore, the short lead-in times before peak expiratory flow rate was measured, both on and off stimulation, were insufficient for improvements in pain or movement symptoms to be observed. The improvement in lung function was, therefore, deemed unlikely to be simply a reflection of the amelioration in the patients' underlying disorder.[24]

The forced expiratory volume in 1 s (FEV1), a lung function measure that reflects airflow in both the upper and lower airway, was unchanged in either group. As peak expiratory flow rate is a more sensitive index of large-airway flow than is FEV1, the researchers concluded that DBS of the PAG and STN predominantly alters upper airway resistance. Alternatively, as the patients were not in respiratory distress and had no existing lung disease, little scope might exist for any further improvement in FEV1. Indeed, the only patient who showed an obstructive lung function profile on spirometry also exhibited a 10% increase in FEV1 on PAG stimulation. [24]

Further study of DBS is required to determine whether this treatment might offer benefits in respiratory diseases associated with dysfunction of airway tone, such as asthma, chronic obstructive pulmonary disease and obstructive sleep apnoea.

Modulation of other physiological systems

DBS also has modulatory and beneficial effects on other autonomically controlled systems. Dysautonomia in patients with PD can manifest as urinary dysfunction with incontinence, frequency and urgency. Increased regional cerebral blood flow to the anterior cingulate cortex and lateral frontal cortex is seen during off-stimulation bladder filling in patients with PD who are undergoing DBS of the STN, in comparison with on-stimulation bladder filling.[97] Animal and human studies alike have shown improved urodynamics with STN

stimulation, whereby bladder capacity is increased and the first desire to void is delayed.[98–100] A similar functional improvement in urodynamics, coincident with normalization of the frontal network cerebral blood flow, was demonstrated during STN stimulation in patients.[97] The site of DBS is important, however, as pedunculopontine nucleus stimulation in a patient with PD has been associated with urinary incontinence owing to detrusor overactivity.[101] This finding is supported by the results of a study in Göttingen minipigs, in which DBS of the pontine micturition centre resulted in increased detrusor pressure as measured by cystometry.[102]

One small questionnaire-based clinical study reported not only a decrease in sweating and bladder-function symptoms such as leak and general satisfaction with bladder performance, but also improved bowel control with stimulation of the STN.[103] Although this finding was based on only a single patient's responses to a questionnaire, other evidence suggests that DBS might improve some aspects of alimentary function. Swallowing can be impaired in patients with PD, and stimulation of the STN is associated with improvements in muscle excursion and timing of muscular contractions during the pharyngeal phase of swallowing.[104] Further evaluation of STN stimulation in a large cohort of patients is required to clearly define the effects of DBS on the alimentary system.

Conclusions

The CAN rapidly influences physiological systems throughout the body. The stimulation of components in this network during DBS can modify the function of cardiovascular, respiratory and even urinary systems. These autonomic effects can manifest as adverse effects of DBS, which are frequently encountered in clinical practice. However, if modulation of this neurocircuitry can be harnessed therapeutically, DBS could have enormous potential to alter autonomic function in patients with dysautonomias. We speculate that various conditions might be amenable to DBS treatment in the future, including dysautonomias in patients with neurological disorders such as PD, or even conditions currently treated by purely medical means, such as orthostatic hypotension and asthma.

Review criteria

The articles for this Review were selected by searching the MEDLINE database, without applying any limits such as language or year of publication. The search terms included: "deep brain stimulation", "DBS", "autonomic", "central autonomic network", "CAN", "cardiovascular", "respiratory", 'micturition", "bladder", "subthalamic nucleus", "STN", "periaqueductal grey", "PAG", and "hypothalamus". Full-text articles were selected and the reference lists used to identify further articles of relevance.

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J. A. Hyam researched the data for the article. J. A. Hyam, M. L. Kringelbach, P. S. Silburn, T. Z. Aziz and A. L. Green provided substantial contribution to and discussion of the content, and to review and editing of the manuscript before submission. J. A. Hyam and M. L. Kringelbach contributed equally to writing the article.