Title: Using Deep Brain Stimulation to Unravel the Mysteries of Cardiorespiratory Control.

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Didactic Synopsis

Major Teaching Points;

- Deep Brain Stimulation (DBS) is a therapy in which electrodes are implanted into the brain to stimulate specific nuclei such as the subthalamic nucleus in Parkinson's disease
- Patients with PD often suffer from 'dysautonomia'; characterized by abnormal autonomic responses such as postural hypotension. DBS has been shown to alter these responses in specific situations
- The ability to stimulate the human brain and record autonomic responses has allowed researchers to understand better the role of brain areas in autonomic control, and to confirm the findings of animal experiments.
- DBS electrodes can be used to record from the brain, allowing us to look at increases and decreases in activity, and determine whether specific areas are related to manipulations that alter autonomic control, eg during exercise.
- Combining DBS research with other modalities such as imaging and EEG may help to increase our knowledge of the neural circuits in humans underpinning autonomic control.

Didactic Legends

Figure 1. This figure shows areas in the brain that are known to be involved in cardiac and/or respiratory control. Areas include the cortex, the diencephalon (basal ganglia), midbrain and brainstem. This suggests that autonomic control is organised in a hierarchy with basic functions such as the baroreceptor reflex terminating in lower areas and the higher areas involved in autonomic changes that occur in complex behaviours

Figure 2. This figure shows the process involved in inserting a DBS system. The electrodes are inserted during surgery by applying a 'stereotactic frame' to the head to ensure accuracy. The coordinates are determined from locating the target on the patient's scan. The complete system consists of brain electrodes connected to a pacemaker in the chest

Figure 3. Microneurography is a technique in which electrical activity in peripheral autonomic nerves can be measured directly using a tungsten microelectrode. This can be done whilst stimulating the brain to see if sympathetic nerve activity is altered.

Figure 4. The pedunculopontine nucleus (PPN) is an area in the brainstem that is used to control gait and imbalance in PD. Stimulation of this area also improves the drop in BP that occurs on standing in some patients. Diffusion tensor analysis (DTI) is a type of MRI scan that looks at connections in the brain and DTI has shown that the PPN is connected to a number of other areas including some that influence autonomic control.

Figure 5. This figure shows that stimulation in one part of the periaqueductal gray area (PAG) – the ventral PAG- decreases BP whereas stimulation in another part – the dorsal PAG – increases BP. The changes are rapid, occurring within a few seconds of the start of stimulation

Introduction

For many decades, the role of the brain in autonomic control has been seen as a 'black box', with peripheral mechanisms elucidated in far more detail. A better understanding of the role of the brain in autonomic control that details how it exerts such control is desirable in order to understand the whole system, and potentially provide more targets for manipulation(128). Advances in neuroimaging combined with deep brain stimulation (DBS) therapy have facilitated a better understanding of the neural circuits underpinning the control of the cardiorespiratory system(108, 190). This review charts the history of DBS as applied to alleviating a number of neurological disorders, whilst in parallel mapping the electrophysiological circuits involved in generating and integrating neural signals driving the cardiorespiratory system such as during exercise. DBS involves insertion of electrodes into an ever increasing number of brain areas for a variety of conditions(194). In situations in which these areas overlap with those that control autonomic functions, there is a unique opportunity to neurophysiologically investigate such areas either by recording *local field potentials* (LFPs) to assess how the area is modulated by exercise and other factors, or by stimulating the area to look at how autonomic function is modulated.

The Central Autonomic Network (CAN) consists of multiple sites from the spinal cord to the cortex involved in autonomic control (figure 1). Important areas exist at multiple evolutionary levels and include the anterior cingulate cortex (ACC))(telencephalon), hypothalamus (diencephalon), periaqueductal grey (PAG)(midbrain), parabrachial nucleus (PBN) and nucleus of the tractus solitaries (NTS)(brainstem) and the intermediolateral column of the spinal cord (IML). The CAN receives afferent input from all over the body and integrates them into a coordinated efferent autonomic (sympathetic and parasympathetic) response. However, the CAN is not a 'silo' operating alone but is richly connected to other systems such as nociceptive, cognitive, motor, as well as the reticular and forebrain monoamine and cholinergic systems involved in motivation, attention, emotion and circadian rhythms(24). Thus autonomic control is complex and is integrated with multiple networks within the brain. This review will not attempt to summarise all studies related to brain stimulation or recording and autonomic control as this would be too large a task. It will concentrate on human studies using DBS, discussing the novel and often unique insights from such studies and also the limitations such as the inability to 'choose' the target for scientific purposes. As the majority of DBS procedures are carried out in patients with Parkinson's disease (PD), dysautonomia in this context will also be discussed. It is also important to recognise the limitations of using DBS as a tool to investigate cardiorespiratory control and these limitations are listed in table 1.

Background 1: Brain structures involved in cardiovascular regulation

Brain control of the cardiovascular system (CVS) can be loosely divided into cortical and subcortical control. The primary viscerosensory cortex receiving afferent cardiovascular information is the insula, and there is evidence of lateralisation of autonomic function. Whilst out of the scope of this review, in general, the right insula has been associated with sympathetic outflow(77) whereas the left side has been associated with vagal functions(66). However, this is probably an oversimplification, as proposed by Thayer and Lane in their 'dynamic systems framework' (239, 240). The insula receives projections from the NTS and other areas such as PBN and hypothalamus.

Descending projections within the CAN include the amygdala and hypothalamus where the latter sends projections to the rostroventrolateral medulla (RVLM). The insula also sends collaterals to the NTS and RVLM and can directly influence cardiovascular function (see (24) for a review).

Another area that has the potential to influence the autonomic system and is also used in DBS for pain control is the ACC (35). Many functions are ascribed to the ACC, including decision-making, cognition, arousal and motor control (20, 124, 219). It has been described as an area that translates intentions into actions(193), and recently implicated in the context of central command (99). Connections from ACC to PAG (7) and hypothalamus (183) may conceivably influence autonomic output. Indeed there is good evidence for this in humans. Pool and Ransohoff in 1949 found that electrical stimulation in humans undergoing psychosurgery caused changes in both cardiovascular and respiratory parameters (200). Other investigators have similarly seen autonomic alterations during both human and animal studies (40, 53, 97, 137, 138, 250). Conversely, exercise and mental stress tasks lead to increased cerebral blood flow in fMRI studies (68) Lesion studies (either cingulotomy or secondary to tumour) have consistently shown reduced sympathetic drive (68, 261) as well as altered perception of breathlessness (196).

The amygdala also plays a role in the control of autonomic responses in that it is part of the limbic system and important for the integration of emotions (especially anxiety and fear) and behavioural outputs, including cardiorespiratory responses(48). The central nucleus of the amygdala projects to the lateral hypothalamus and other areas in the CAN such as the PBN, NTS , and the dorsal motor nucleus of the vagus nerve (DMNX)(46). It also receives afferents from the baroreceptors, ACC and insula (46, 47). Electrical stimulating the amygdala causes a differential response depending on whether the animal is awake or under anesthesia; in the awake animal, stimulation causes a pressor response whereas it causes a depressor response when the animal isunder anaesthesia or asleep(90, 92, 96) The prefrontal cortex exerts a tonic inhibition over sympathetic-mediated inotropic and vasoconstrictive drive in order to maintain a fine balance of cardiorespiratory control. For example, GABAergic inhibition via prefrontal-amygdala projections suppresses heart rate (HR) via multiple mechanisms such as increased vagal outflow via the NTS or inhibition of sympathoexcitatory RVLM neurones (215, 239). Thus the prefrontal cortex is an important component of Thayer and Lane's Neurovisceral Integration Model of physiological, affective and cognitive processes that are part of goal-directed behaviour(240)

Multiple subcortical areas are important in cardiorespiratory control. The hypothalamus not only 'mediates' forebrain autonomic responses (46),but also integrates responses with circulating volume via its hormonal influence on the kidney (controlled by the paraventricular nucleus (PVH). The lateral hypothalamic area (LAH) can produce depressor or pressor effects depending on the subregion stimulated and projects to insula and the IML in the spinal cord (4, 5, 49) (important for sympathetic output). Another key subcortical area is the PAG that is coupled to non-autonomic functions including analgesia (45) , fear,anxiety (45), vocalisation (37), and reproductive behaviour (246). Columns of the PAG are functionally distinct and opposite. Activation of the dorsomedial and dorsolateral columns evoke 'fight or flight' responses, compared to passive coping responses evoked by stimulation of the lateral and ventrolateral columns (31, 44). Similar responses are found in humans (111). The primary role of the PAG is to act as an integrating control system in the context of environmental stress or pain, although emerging thinking suggests it is also involved in controlling the cardiorespiratory response to exercise (see below).(190)Brainstem areas rich in

cardiorespiratory control include the pons and medulla. In the former, the PBNl and Kolliker-Fuse (KF) nuclei in the dorsal brainstem are known to have respiratory modulating functions that cause hyperpnea and apnea (50), which are also linked to locomotor-respiratory entrainment (100). Regarding cardiovascular control, the NTS, Nucleus Ambiguus (NA), DMNX and RVLM are important for beat-to-beat control. Whilst these medullary regions are vital for cardiorespiratory control, they are not currently subject to human stimulation, but discussed in greater detail elsewhere (24, 70, 114, 211)

Background 2: The History of Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a therapy in which fine electrodes (typically measuring less than 1.5mm in diameter) are passed into the human brain via a surgical operation (14, 194) (figure 2). In order to pass electrodes accurately to the brain target of interest, a 'stereotactic frame' is attached to the exterior of the head (using sterile screws that grip tightly to the scalp). The patient's brain is imaged in the frame so that the region of interest can be assigned X, Y and Z coordinates relative to the frame. A small hole (known as a 'craniostomy') is then drilled in the skull and the electrode is passed through a mounting on the frame to the desired coordinates. The electrodes are passed under the skin and connected to extension leads that are in turn connected to an 'implantable pulse generator' (IPG) (similar to a pacemaker) that is placed in a subcutaneous pocket, often just below the clavicle. There are numerous variations of the procedure such as the use of robots (with or without a frame), microelectrode recordings to help localise the target neurophysiologically, awake testing or the full procedure under general anaesthetic, and much controversy regarding patient and target selection. However, the fundamental principal remains universal – the harnessing of electrical energy to alter the function of a brain nucleus or tract in order to reduce the symptoms of disease.

The use of 'stereotaxy' (moving towards a position in 3D space) has allowed scientists to explore the brain accurately for generations, such as the use of a frame by Dittmar in 1873 to explore the medulla in an animal model (33, 78). Pertinent to this review, Dittmar worked in Carl Ludwig's laboratory in Leipzig, along with Owsjannikow to perform precise lesioning experiments used to explore the vasomotor center in the medulla oblongata. Their description of this ventrolateral medullary region important for vasomotor tone and reflexes is the earliest and most precise description of the *rostroventrolateral medulla* (RVLM), although the term was not coined until over 100 years later(221). Whilst a number of frames were adapted for human use such as Zernov's *encephalometer* in 1889(262), none of these utilized Cartesian coordinates or became developed enough to contribute to modern human stereotaxy(33). True stereotaxy utilising Cartesian coordinates in humans was first made possible and became developed to modern use with an adaptation of an earlier frame by the American experimental neurologist, Ernest A. Spiegel, and his collaborator surgeon, Henry T. Wycis(231). The Spiegel and Wycis frame built on the 'Horsley-Clarke' frame(218) that was designed as a collaboration between the British physiologist Robert Henry Clarke and the pioneering Queen's Square Neurosurgeon, Victor Horsley for use on primates and cats. Spiegel and Wycis not only enlarged the frame, but used a plaster mould that was bespoke for each patient's head. In this pre- CT era (1947), they used air ventriculography in which air was injected into the cerebral ventricles and targets with 'known' coordinates relative to structures such as the anterior and posterior commissures could be selected. Their first cases used the apparatus to

make lesions in the dorsomedian thalamus (part of the limbic pathway) to replace the more common prefrontal leucotomy(231). The success of Spiegel and Wycis was mirrored by many surgeons around the World, leading to further important developments including the introduction of an 'arc' to the frame system by Lars Leksell in 1949(154). The arc allowed the surgeon to plan the *trajectory* to the target (rather than just the target itself) which meant that important structures leading to the target such as blood vessels could be avoided.

The advent of human stereotaxy allowed for the precise 'lesioning' of brain targets to treat diseases such as Movement Disorders. A prototypical example is that of 'pallidotomy'. In 1952, a US surgeon, Irving Cooper discovered that ligating the anterior choroidal artery could lead to improvement in tremor and rigidity associated with PD(61). Cooper later conceived the idea that direct lesions of the basal ganglia such as stereotactic injection of absolute alcohol into the medial globus pallidus interna (GPi) would be better, and he performed many such cases(60). He later developed this into *thalamotomy* involving the ventrolateral thalamus, the main output tract of the GPi, as this worked better for the tremor than GPi lesions(62). *A* number of different procedures were spawned in various places internationally. Whilst these procedures involved accurate stereotactic placement of cannulae for injection of various substances, and later rigid electrodes that could be heated up to create a lesion (so called 'radiofrequency lesioning' such as pioneered by William Sweet for the treatment of chronic pain in 1960(238)) they did not involve the chronic placement of implantable electrodes whose electrical outputs could be titrated against symptoms and the effects reversed if necessary. This paradigm shift may be attributed to the work of many people, but one of the foremost pioneers was Robert Heath at the Tulane Medical Centre in New Orleans in the 1960s. Heath was a psychiatrist who concentrated his work on patients with severe, refractory symptoms who had often been institutionalised. Whilst in general, the ethics of the 'Tulane Medical Experiments' have been called into question in a program partly funded by the CIA to look at 'mind control' (see Valenstein(245)), many targets were investigated such as the septal area for severe depression. The role of the septal area in enhancement of pleasure was largely elucidated by the neuroscientists, James Olds and Peter Milner in the 1950s in experiments that demonstrated that a rat would run across a red hot plate that it would not otherwise touch, in order to acquire septal stimulation(182). Heath used these findings to justify septal stimulation in depression. His work was clearly influenced by others such as Delgado in Spain who had performed pioneering experiments in bulls and chimpanzees amongst other animals as well as humans and demonstrated that chronic stimulation was possible(72-74).

Whilst much of Heath's work was experimental, his ability to perform chronic human stimulation was hampered by the lack of miniaturized technology. For example, patients had to connect to a large external battery and received intermittent stimulation. As technology progressed, fully implantable systems became available, manufactured by the American company, Medtronic. The first major trials using DBS attempted to show that chronic, refractory pain could be successfully treated(57), following a number of large case series in the 1970s(126, 209). Whilst the use of DBS to treat pain has many advocates today, the large Medtronic trials (1976 and 1990) were ultimately unsuccessful for a variety of reasons including poor patient recruitment, withdrawal of the electrode in one trial, and patients being lost to follow up(57). The trial protocols essentially amounted to grouped case series with follow up of one year and were industry sponsored – the aim being to satisfy the Food and Drug Administration requirements for approval. Additional problems included heterogenous case mix, poorly defined recruitment criteria, subjective and unblinded assessment of

outcomes, and small numbers per centre(194). The use of DBS for pain therefore remains controversial. Regarding DBS for movement disorders, there were a number of people around the world working on the concept, such as Natalia Bechtereva at the Polenov Institute of Neuroscience in Leningrad, who performed chronic electrode implantation (that she termed *therapeutic Electro-Stimulation)* in the mid-1960s, targeting the motor thalamus for PD (see(115) for a summary). In the West, in the 1970s, Jason Brice from the UK used DBS as a treatment for refractory essential tremor(36) and pioneering work by Benabid in the 1980s put DBS on the map again(21-23). This was coupled with at least two other major factors. First, many of the lesional therapies for PD (PD) were superseded by the introduction of the drug, Levodopa, in 1960 but as the disease progressed it became clear that increasing doses of levodopa met with intolerable side-effects and an alternative was required. Second, seminal work in Parkinsonian primates led to the investigation of a new target – the subthalamic nucleus (STN) – that appeared to alleviate not just the tremor in PD, but also the bradykinesia, rigidity, and some of the other symptoms that were not alleviated by thalamotomy alone(11, 29).

Modern DBS is a rapidly changing field that has built and expanded on the well-established treatment of movement disorders and has incorporated the exponential growth in neuroscience and associated techniques such as functional imaging, as well as developments in technology and computing. Many 'new' indications are based on either physiology from animal experiments (such as DBS for refractory temporal lobe epilepsy(88, 247) and psychiatric disorders, such as obsessive compulsive disorder(75, 205)) or on functional imaging studies. Examples of the latter include DBS for depression in which the subgenual cingulate gyrus (Brodmann area CG25) was identified as being overactive in depressed patients compared to controls. Subsequent DBS studies have utilized this target(168, 222) and although the initial studies were 'successful', randomised controlled trials are yet to prove efficacy(145). Technology advances include 'directional' electrodes that are segmented (as opposed to the standard circumferential 'ring' electrode) which allow for directing the current to the nucleus of interest and avoiding unwanted side-effects. Much research is being devoted to different electrical waveforms, the use of 'closed-loop' stimulation in which the output is influenced by either brain recordings or an external physiological biomarker such as electromyography (EMG), and rechargeable battery technology. Indications under investigation include a myriad of psychiatric disorders (Tourette's syndrome, Anorexia Nervosa, Obsessive Compulsive Disorder, Depression, Addiction, Schizophrenia), Dementia, Epilepsy, Pain, Tinnitus, Autonomic disorders and many more. This rapid expansion of interest in the technique means that researchers have an unprecedented opportunity to study the effects of DBS on an ever increasing number of brain areas. There are two important concepts here. First, by stimulating a specific brain area, it is possible to look at the 'lesional' effects (using high frequency stimulation) or other effects (lower frequency) that help elucidate how a specific brain area functions in both health and disease. Second, one can measure electrical activity through DBS electrodes (such as LFPs) that can inform us as to how a specific area responds in certain situations. By combining these two techniques we can shed light on the neurocircuitry underpinning brain function, such as that involved in cardiorespiratory control.

Dysautonomia in Parkinsonian Disorders and the effects of DBS on cardiorespiratory function.

Parkinson's disease (PD) is the most common condition treated using DBS, with over 150,000 cases having been performed worldwide(116). It has a prevalence of 100-200 per 100,000 in the general population(1) and 1500-3000 per 100,000 in the over 65 year age group. It is characterised by

degeneration of the Dopamine-producing cells that project from the *Substantia Nigra pars compacta* (SNpc) to the striatum. Dopaminergic pathways in the brain are numerous and the disease produces a wide spectrum of phenotypes. Whilst the best documented symptoms relate to the basal ganglia control of movement leading to tremor, rigidity and bradykinesia (slowness of movement) as well as poor postural control, there are many 'non-motor' symptoms that vary from patient to patient. These include sleep disorder(123), psychiatric (such as hallucinations, psychosis, depression and impulse control disorders(12)), pain(93), dementia(95), and bulbar symptoms(225). However, a large proportion of non-motor symptom relate to autonomic dysfunction. These include postural hypotension, bladder and bowel dysfunction, sweating abnormalities, and ophthalmic dysfunction(136). More recent reports suggest that respiratory function is also deranged (13).

Cardiovascular autonomic abnormalities are perhaps the most extensively studied 'dysautonomias' in PD. Specifically, orthostatic hypotension (OH) (defined as a reduction in systolic blood pressure (SBP) of at least 20mmHg or diastolic blood pressure (DBP) of at least 10mmHg or symptoms of cerebral hypoperfusion within three minutes of standing(251)) has at least three underlying pathophysiological mechanisms(133) . These include the loss of cardiac sympathetic post-ganglionic noradrenergic nerves that is almost ubiquitous in PD and is demonstrable using ^{18}F-dopamine (^{18}FDA) positron emission tomography (PET)(101) and at post-mortem, extracardiac noradrenergic denervation, and loss of the arterial baroreflex. The latter includes loss of both sympathetic and parasympathetic components. The fact that PD is characterized largely by loss of the noradrenergic component of the autonomic nervous system (rather than the cholinergic part) fits with the fact that dopamine is a precursor to norepinephrine and that dopamine is depleted in PD. However, cholinergic dysfunction leading to dysautonomia in the parasympathetic part of the autonomic nervous system (ANS) is also present to varying degrees in the form of sweating abnormalities and constipation(233)although there is controversy as to whether the latter is due to brain or gut pathology(185). Jain and Goldstein have pointed out that many of the other non-motor abnormalities in PD, whether associated with PD or otherwise, are also associated with cardiac sympathetic denervation, including Rapid Eye Movement (REM) behaviour disorder (RBD) and dementia(133). A putative pathophysiological mechanism relates to studies that have shown reduced intraneuronal vesicular uptake of catecholamines in Lewy body diseases (including PD) leading to accelerated neuronal catecholamine loss and possible toxicity due to increased cytosolic levels of catecholamines(103).

The pertinent question related to this review is what proportion of the cardiovascular dysautonomia seen in PD is due to peripheral pathological mechanisms such as those outlined above, and how much can be attributed to a loss of top-down control from the brain itself secondary to degeneration in areas such as the striatum or brainstem? Whilst there is a poor correlation between striatal dopaminergic loss and cardiac sympathetic denervation(102, 104), another potential mechanism – the baroreceptor reflex(81) – is more likely to be affected by brainstem degeneration as it relies on brainstem reflex loops for its function(113).

The baroreceptor reflex can be influenced by higher brain function. This was first demonstrated by Moruzzi in 1940(176) who reported that the carotid sinus reflex could be inhibited by stimulation of the anterior vermis of the cerebellum. This work was followed by a number of studies in the 1960s exploring the relationship between cardiorespiratory changes in the periphery induced by brain stimulation and the baroreceptor reflex modulation. For example, Wilson stimulated both the

perifornical area and the hypothalamus and found that whilst stimulation led to increases in ABP and respiration, there was 'no marked difference in the ease with which the baroreceptor reflex caused bradycardia and reduction of blood pressure in control and stimulation experiments. This led the authors to conclude that the brain stimulation and baroreceptor effects were independent but 'algebraically summed'.(118, 257), Smith and Nathan explored stimulation of the inferior olive, an area that receives fibres from rostral brainstem areas that influence cardiovascular control(228). Whilst stimulation did not induce cardiovascular responses *per se*, they found that it inhibited the depressor component of the carotid sinus reflex. Other areas found to influence the reflex included the diencephalon(230).Reis performed decerebrations, , brainstem transections and electrical stimulations to further understand the relationship between supramedullary areas and the baroreceptor reflex(206-208). Examples of Reis' experiments include a series of studies in cats in which transection of vagi and carotid sinus nerves leads to a rise in BP due to the lack of reflex. However,subsequent decerebration led to a fall. When the experiments were performed in reverse, decerebration leads to a slight fall in BP, which is unaffected by subsequent nerve section. They concluded that 'rostral brainstem structures principally influence tonic brainstem mechanisms sub serving baroreceptor reflex excitability rather than those maintaining normal blood pressure. Other important work by Coote in the 1970s, based on Hilton's previous work of the 1960s(118-120) demonstrated that stimulation of points in the defence area (part of the PAG) caused inhibition of the reflex(63). Stimulation of the hypothalamus, in proximity to but outside the defence area did not abolish the sympathoinhibitory or depressor effects of baroreceptor activation, despite this area causing an increase in BP similar to those seen with defence area stimulation. Inhibition of reflex bradycardia seen with defence area stimulation was however still present. The authors postulated that the 'less localised changes' seen in the latter area are the result of an augmented increase in central inspiratory drive that leads to inhibition of the vagal flow to the heart. In a similar way to lesional and electrical studies in animals, pathology in PD leading to OH is associated with a decreased baroreflex sensitivity (BRS)(32).

Multiple System Atrophy (MSA) is a similar neurodegenerative disorder that is associated with brainstem degeneration(151), and dysautonomia is often a dominant feature of the disease. Patients with MSA do not generally exhibit cardiac sympathetic denervation as seen in PD(133) whilst the baroreflex is still significantly reduced compared to controls, albeit with slightly different characteristics(213). The common pathological characteristic between the two diseases is the aggregation of abnormal α-synuclein throughout the nervous system(42) (both peripheral and central) and, along with other α-synucleinopathies such as *dementia with Lewy bodies* and *pure autonomic failure (PAF)*, the distribution of α-synuclein throughout the nervous system provides a predictor of the autonomic phenotype of the disease(170). In MSA, the primary hallmark is the presence of oligodendroglial cytoplasmic inclusions of α-synuclein(131, 188) and the degeneration of preganglionic autonomic neurons of the brainstem and spinal cord(25, 184) account for many symptoms such as OH that has been postulated to be due to degeneration of neurons in the RVLMRVLM(28). Similarly, degeneration within the pontine micturition centre (PMC) may be the cause of detrusor hyperreflexia, urethral sphincter weakness and failure of detrusor contraction leading to the urinary urgency, incontinence and retention seen in MSA(26, 59, 258).

The difficulty with using pathology to infer how specific brain areas (or networks) influence cardiorespiratory control is that neurodegenerative diseases rarely affect one specific brain area and disease phenotypes are often heterogenous. However, DBS provides a unique opportunity to study

the neurocircuitry of cardiorespiratory control both in terms of the control of physiology (albeit in a disease state) as well as to study the effects of stimulation in humans. Thornton et al(241) looked at the effects of acute stimulation in patients undergoing DBS for either PD or dystonia. High frequency stimulation of the motor thalamus, STN and SN all caused modest rises in mean arterial pressure (MAP) and (HR) whereas stimulation of the GPi did not. Whilst stimulation of the same areas is associated with a facilitation of movement, the cardiovascular changes were not dependent on movement feedback from exercising muscles. The authors hypothesised that subcortical command may be involved in 'parallel activation' of the locomotor and cardiovascular systems. Previous evidence for such a parallel activation comes from studies that dissociate exercise itself from the intention to exercise i.e. the 'central command' from the brain exists without feedback from exercising muscles (see below for details). For example, a human's perception of exercise rather than the exercise itself can determine the cardiorespiratory response(172, 174, 242). Elaborate experiments in humans have shown comprehensively that muscle feedback is not necessary for the response, such as in hypnotically induced subjects who think they are exercising when they are not(174, 242) , and in paraplegics attempting to lift a foot, in which bilateral insular cortex is activated(179) along with cardiovascular changes (the insular cortex is not known to receive afferents from exercising muscles(121, 122)).

As well as parallel activation of movement and cardiovascular systems, within cardiovascular control *itself* there is evidence of differentiated modulation of central sympathetic outflow via the baroreflex(160). The main evidence for this is that frequency and intensity of central sympathetic nerve traffic have been shown to be controlled independently by the arterial baroreflex(160, 165, 237). This has been hypothesised to occur at two central nervous system locations, one that determines whether or not a burst of sympathetic nerve activity will occur, and another at which the strength of the sympathetic burst is determined(143). Sverrisdottir et al(236) combined the technique of microneurography, that allows direct recording of real-time sympathetic activity, with stimulation of brain areas in human subjects undergoing DBS (figure 3). One patient group were patients with PD undergoing DBS of the STN. The investigators found that stimulation of the most dorsal STN targets (c.f. ventral targets) improves baroreceptor sensitivity (BRS) to the vasculature in those with accompanying dysautonomia. In a second group of patients with chronic pain, stimulation of the dorsal or ventral PAG resulted in a differentiated sympathetic discharge pattern and haemodynamic response (this will be discussed in more detail below in the context of the midbrain PAG).

Clinical Autonomic Effects of DBS in PD and MSA

The clinical effects (as opposed to purely physiological effects) of DBS on autonomic function in Parkinsonian disorders provides some insight into how neurocircuitry can be modulated to reduce dysautonomia. Priori et al studied the non-motor effects of STN stimulation in a small group with PD(201). The authors found that when the DBS system was turned off, the sympathetic skin response decreased in amplitude and increased in latency. Plasma renin activity increased with DBS 'off' but its modification with postural changes and BP was not significantly different between DBS On and Off. This study did however provide some intriguing insights into how DBS may alter autonomic function. There have been many publications since the Thornton and Priori studies

looking at the effects of STN stimulation on the ANS but the results are varied and often conflicting (82, 91, 235, 243, 248). For example, a study by Ludwig in 2007 demonstrated that STN stimulation affects cutaneous sympathetic vasoconstriction but did not significantly affect cardiovascular ANS function(159). This study, however, highlights the common problem with many such studies. Specifically, recruitment number is often very low (often 10-20 subjects), the patients' disease phenotypes are heterogenous, autonomic dysfunction is often not well characterised at baseline, and levodopa – the most common drug used to treat PD – itself has a significant effect on ANS function, such as causing a reduction in BP(82, 178) . In the Ludwig study, levodopa significantly reduced HR and BP at rest and enhanced orthostatic hypotension (OH). Regarding OH specifically, Bunjo et al(39) summarised fourteen studies assessing the effects of DBS on OH in PD and cautiously concluded that the majority of studies demonstrate that OH is 'not worsened' by DBS of the STN. In addition to stimulating the STN, recording electrical activity from the STN has provided some evidence that it plays a role in autonomic control. For example, Coenen et al found that administration of the drug metoprolol that lowers HR and BP leads to decreased spiking(56).

The majority of studies on the effects of DBS on autonomic function in PD concentrate on the STN, both because it is a common target, and few studies have shown changes in autonomic parameters with stimulation of the other common target, the *GPi(39, 241)*. A notable exception, however, is bladder function that may improve with GPi DBS(173) and recordings from human GPi demonstrate that the it is involved in the processing of bladder sensations, at least in PD(212). However, a more recently used target, the *pedunculopontine nucleus* (PPN) may have a greater effect on strengthening autonomic reflexes than the STN (figure 4). The PPN lies laterally at the level of the cerebellar decussation in the pons and is used primarily to treat axial and gait symptoms in PD(199). The PPN is part of the *reticular activating system* and in animals contains the mesencephalic locomotor region, stimulation of which increases mean ABP in animals(54, 80). Cholinergic PPN fibres project to the RVLM(259), an area that is key in the central regulation of ABP (70, 211). Furthermore, chemical activation of the PPN in anaesthetised rats increases sympathetic nerve activity, BP and the baroreflex in addition to muscle activity (measured using electromyography)(186). A recent study in PD patients by Hyam et al(130) demonstrated that PPN stimulation reduces the orthostatic reduction of BP with tilting and identified a combination of associated physiological variables such as increased pulse pressure and dP/dt (the rate of rise in BP that is associated with cardiac contractility) (see also figure 4C for an example). These changes in the BP reduction are clinically meaningful and patients anecdotally report less dizziness on standing. These changes, taken together, suggest that PPN stimulation exerts its effect by modulating both peripheral and central components of the cardiovascular system. PPN stimulation also reduced baroreceptor sensitivity, implying top-down interference with the baroreflex. The exact mechanisms of how PPN stimulation alters cardiovascular function warrants further investigation for a number of reasons. Firstly, the number of subjects in the existing studies are very low (limited by the availability of these relatively rare cases). Second, DBS affects a volume of tissue around the electrode - known as the *volume of tissue activation* (VTA) – which can be a couple of millimetres in radius, depending on the amplitude of stimulation. With the high density of nuclei in the brainstem, it is possible that other neighbouring nuclei are being stimulated, rather than PPN, such as the PBN throughout its length or the locus coeruleus caudally, both nuclei known to have autonomic effects(211). Recent electrodes design includes the advent of 'directional electrodes' in whichthe circumferential 'ring' electrodes are segmented to allow current to be greater in particular directions. Using these, it may

be possible to dissect out electrophysiologically whether areas adjacent to the PPN are responsible for autonomic changes rather than the PPN itself. Further mechanistic studies are also required to elucidate pathways involved caudally to PPN. Sverrisdottir et al tested a single subject with PPN stimulation, recording muscle sympathetic nerve activity (MSNA) via microneurography of the common peroneal nerve(236) but found no change in MSNA with stimulation. However, the subject in question did not exhibit a change in systolic BP with stimulation. Study of a larger number of patients would be useful to determine whether the MSNA changes in those in whom PPN stimulation induces a change in BP.

Regarding the effects of DBS in MSA, the majority of cases have involved stimulation of the STN for treatment of the movement disorder (motor aspects) and in general, this has been performed in the context of the investigators not realising that the diagnosis is MSA but assuming it is PD(169). This is because MSA can be difficult to diagnose pre-mortem and in the early stages the symptoms are often similar to PD, with no diagnostic test being 100% sensitive for one of the other. MSA may reveal itself later as the patient develops dysautonomia and other features and rapidly deteriorates. The generally accepted advice is not to perform DBS in these patients, despite some studies showing early improvement in motor symptoms(169). None of these studies (comprising single cases or small series) have robustly looked at autonomic symptoms, but have described the onset of autonomic symptoms not improved by DBS. However, with the findings described above, the STN would not be the obvious choice for the amelioration of dysautonomia and the authors would speculate that it is possible that PPN stimulation may have a much more significant effect on autonomic symptoms and gait abnormalities.

The midbrain Periaqueductal Gray Area

The *periaqueductal gray area* (PAG is contiguous with the periventricular gray (PVG) rostrally, andin the human, is an approximately curved cylindrical shape whose axial area has a diameter of around 5mm. It surrounds the cerebral aqueduct of Sylvius that joins the third and fourth ventricles. The PAG is involved in a surprising number of functions including vocalisation(37, 152), analgesia(86), fear and anxiety(177), and even reproductive behavior(246). As early as 1935, Kabat studied a number of areas in the brain of the cat and amongst his findings, demonstrated that PAG stimulation can alter BP(139). Several decades later it emerged that the PAG is divided into four longitudinal columns(44). The cardiovascular changes have most often been described as a component of an integrated ‘defence reaction’ whose phenotype depends on which columns are stimulated. For example, dorsomedial or dorsolateral columns subserve an active ‘fight or flight’ response with associated hypertension and tachycardia(43, 79, 158) and non-opioid mediated analgesia(167). On the other hand, stimulation of the lateral and ventrolateral columns causes ‘passive’ coping responses such as hypotension and bradycardia(135, 157), opioid-mediated analgesia(87), and freezing behavior(76).

Both rostrally and caudally, the PAG is richly connected to many areas that are important in autonomic control. Rostrally, the PAG has reciprocal connections to the anterior hypothalamus(41), thalamus(149), amygdala, prefrontal cortex and insula(15, 210) PAG neurones project caudally to cardiac vagal preganglionic neurones in the NA, the DMNX, and the NTS(84). In addition, descending serotonergic and adrenergic pathways that influence sympathetic function project to the

rostroventromedial medulla (raphe magnus and gigantocellular nucleus), the RVLM, locus coeruleus, and the pontobulbar reticular formation(84, 181). Cardiovascular reactions elicited by PAG stimulation can be altered by attenuation of these areas(142). With both rostral and caudal connections, there is specificity with particular columns of the PAG(41, 83) and it is likely that the PAG acts as integrator between higher cortical function (such as emotional reactions to environmental situations) and the necessary activation of the autonomic nervous system including cardiorespiratory responses.

PVG/PAG stimulation has been used as a treatment for chronic refractory neuropathic pain for over four decades(30, 34, 126, 209). Whilst the use of DBS for chronic pain has remained controversial due to lack of class A evidence (trials using DBS devices are expensive and the patients numbers are relatively small), it provides a unique opportunity to study the effects of neuromodulation of the midbrain in awake human participants and to study the effects on physiology including the cardiovascular system. In 2005, the authors demonstrated in 15 subjects that PAG stimulation leads to consistent changes in ABP and the effects are predictable and specific to the columnar location of the electrodes(111). Ventral stimulation causes a consistent depressor response (similar to that in rodents) whereas dorsal stimulation causes a pressor response. With dorsal stimulation, two subjects experienced nausea, sweating and anxiety in association with increased BP, similar to the findings of Nashold(177) and Young and Rinaldi(260) who described dorsal PVG stimulation evoking doom, anxiety, fear and agitation, presumably related to the fight or flight response. Whilst dorsal PAG stimulation may, in a small number of subjects, cause unwanted side-effects, it can also be used for beneficial effect in patients with severe OH(110). OHis OH is present in up to 20% of people over 65 years of age, it can lead to troublesome symptoms including loss of mobility, and its treatment can lead to nocturnal hypertension with associated increased risks of stroke and myocardial infarction(141, 214). In the normal subject, the baroreceptor reflex prevents OH i.e. pooling of blood in the lower extremities and splanchnic circulation upon standing results in a decreased venous return to the heart, a transient decrease in BP and a compensatory decrease in parasympathetic activity via the carotid baroreceptor reflex(94). Stimulation of the dorsal PAG in the situation of OH or orthostatic intolerance attenuates the drop in BP and leads to an increase in baroreceptor sensitivity and subsequent upregulation of both the cardiac and peripheral sympathetic nervous systems(110).

Although DBS of the PAG has not been used specifically for the treatment of OH, it has been used for the treatment of refractory hypertension as first mooted by the authors in 2007(109). Patel et al subsequently reported a case of a 55 year old male with severe post-stroke neuropathic pain and resultant severe refractory hypertension (up to 265/96 mmHg) in whom PAG DBS was performed(189). Whilst the patient initially had a good response, ultimately the stimulation-induced analgesia did not last but at 33 months after surgery, his BP was within normal limits (118/70) and turning off the stimulation at 27 months led to a temporary increase. The same investigators subsequently treated a 54 year old female with PAG DBS for de novo refractory hypertension(180) who had hypertension of unknown cause. She had tried eight antihypertensive medications, chronic baroreflex activation therapy, and renal sympathetic denervation, all to no avail. Her presenting BP was in excess of 300/170mmHg. DBS initially significantly reduced her BP to 170/109 and the effect lasted for over three months. However, whilst long-term BP was significantly lower than at presentation, at two years, it remained around 230/150 mmHg. MSNA recordings demonstrated that the reduction in BP was associated with a reduction in efferent sympathetic nerve activity.

The mechanism of stimulation induced cardiovascular changes secondary to PAG stimulation was investigated by Sverrisdottir et al. using microneurography to record MSNA (236). Ventrolateral stimulation increased vascular BRS, and MSNA burst frequency and burst index reduced. MSNA burst amplitude distribution demonstrated a leptokurtic form indicating a greater number of low amplitude bursts than medium to high amplitude bursts. Stimulation was also associated with a reduction in ABP and HR. It is likely that there is interaction between pain and cardiovascular regulatory systems in the PAG and there is an association between increased BP and decreased pain sensitivity(38, 203). It has been suggested that baroreflex control of cardiovascular regulation is in some way connected with antinociception in hypertensive subjects(217) although this phenomenon is poorly understood. Stimulating the NTS, the first synapse of baroreceptor afferents(232) elicits antinociception through projections to PAG and the RVLM. Sverrisdottir concludes that PAG induced baroreflex inhibition of central sympathetic outflow and this is concordant with the hypothesis of a baroreceptor-mediated antinociception through inhibition of the endogenous opioid system(217).

Despite also leading to effective pain relief, dorsal PAG stimulation behaves differently in that it causes MSNA burst amplitude to shift to a mesokurtic form (a greater number of medium to high amplitude than low amplitude bursts), a decrease in spontaneous BP variability, and no change in burst frequency(236). This pattern of changes is similar to that seen in conditions associated with anxiety and stress(252) and during an arousal stimulus (causing mental stress). This fits with the role of dorsal PAG in the fight or flight reaction and its association with fear. This active coping response, at least in rodents, is associated with endogenous non-opioid analgesia, increased HR and ABP(167). Pereira et al have disputed this(197). Using naloxone, an opioid antagonist, they demonstrated that electrical activity in the gamma frequency range increases with the administration of naloxone and subsequent loss of stimulation produced analgesia and conclude that the change in activity in dorsal PAG is likely to be related to pain processing. Sims-Williams et al used [^{11}C]diprenorphine positron emission tomography to explore the analgesic mechanism of PAG DBS(226). They found that DBS of the lateral and dorsolateral PAG induces endogenous opioid release from a cluster in the dorsal PAG, reinforcing the notion that the dorsal PAG mediates analgesia via an opioidergic mechanism. Whilst this study does not prove a difference between ventral and dorsal PAG stimulation, it reinforces the view that stimulation invokes separate mechanisms.

Heart rate variability (HRV) is a simple method to measure the balance between sympathetic and parasympathetic control. There are many methods to evaluate HRV, one method being to use a Fast Fourier Transform analysis to look at the underlying frequencies making up the continuously measured HR. High frequency (0.15-0.4Hz) power can act as a surrogate marker of vagal parasympathetic tone(140). Low frequency (0.04-0.15Hz) was initially thought to be related to sympathetic activity but is probably influenced by a mixture of both sympathetic and parasympathetic tone(187, 202). In non-stressful conditions, the LF component is probably influenced more by parasympathetic activity, thus pharmacological vagal blockade abolishes it(162). Changes in LF/HF ratio give clues to alterations in sympathetic vs parasympathetic balance and the ratio is altered in various diseases such as heart failure, diabetes mellitus and myocardial infarction(150)

(171, 216). Pereira et al investigated the effects of PAG DBS on HRV(195) and found that ventral PAG stimulation significantly increased the HF power and decreased the LF/HF ratio of HRV, demonstrating that stimulation alters the balance between the two systems. Secondly, the changes

in HRV were not induced by dorsal PAG, adding to evidence of differentiated cardiovascular control between ventral and dorsal PAG in the human. Furthermore, diffusion tensor analysis (DTI) showed that ventral PAG projected to the dorsolateral medulla whereas dorsal PAG did not.

Whilst the PAG is not classically linked to degenerative disease, it is likely that pathology within it contributes to the dysautonomia seen in some neurodegenerative diseases. For example, Benarroch found Dopaminergic cell loss in the PAG in MSA and Lewy Body Dementia(27). Sitsapesan et al(227) reported a case of a patient undergoing PAG DBS for chronic neuropathic pain who subsequently developed a progressive neurodegenerative process involving the brainstem. Stimulation before the neurodegenerative process resulted in reduction in BP and other cardiovascular changes as previously described. However, after the neurodegenerative process had been established, the response to stimulation was altered, suggesting that the PAG (or its connections to adjacent areas) involved in cardiovascular responses were altered. Similar work in patients with PD has shown parallels between the differential cardiovascular effects of dorsal versus ventral STN stimulation in PD and PAG stimulation in pain(236). Given that there are known connections between STN and PAG, it is likely that at least part of the dysautonomia seen in PD is linked to efferents to PAG.

The Role of DBS in Identifying central circuits involved in the cardiorespiratory response to exercise

For over 100 years, evidence has emerged that the higher centres(148) and information from working muscle(134, 263) regulate the breathing and cardiovascular response to exercise. The concept of 'cortical irradiation' first proposed by Krogh & Lindhard(148) suggested that higher centres were involved in the anticipatory response to exercise. Asmussen et al performed experiments in the 1960s in which they used curare to block exercising muscle and found that despite the lower intensity of muscle activity, the ventilatory responses increased in association with increased effort(9, 10). They concluded that the increase was due to a 'nervous factor' and postulated that this could have a central or peripheral origin. The importance of neural controlwas further refined by Goodwin, McCloskey & Mitchell(107) where they elegantly demonstrated the concept they termed 'central command'. Using tendon vibration, they showed that the HR, BP and ventilatory response to exercise could be altered during constant load isometric exercise if either the triceps or biceps tendon was stimulated. That is, if the triceps was contracted, tendon vibration of the biceps muscle would cause reflex inhibition. To maintain a constant work rate the subject would have to put in more effort, which resulted in a greater cardiorespiratory drive. Conversely, the opposite cardiorespiratory response occurred when the tendon of the triceps muscle was vibrated as the subject perceived the effort to be less in order to maintain a constant work rate. Studies using hypnotic suggestion of exercise or altered perception of exercise intensity have evoked similar respiratory responses (69, 175, 242), although whether imagining exercise under hypnosis simulates real exercise central command is a matter of debate.

The results from these studies were phenomenological with no neuroanatomical basis as to where the command neurons reside, but nevertheless they clearly highlighted the power of the brain in driving a behavioural response. So where are the command neurons? The first attempt to define the neurocircuitry came from anaesthetized animal studies in the cat(198) and dog(229) that targeted the hypothalamic region. Here they showed that electrical stimulation could increase sympathetic discharge and ABP, mimicking the exercise response. These observations were further refined by

Eldridge et al(80) in decorticate cats who showed that stimulation of the mesencephalic locomotor region (including sub thalamic nuclei) caused a parallel increase in breathing, BP and HR that was coupled to locomotion. Importantly they demonstrated that the cardiorespiratory response was still present when afferent signals from skeletal muscle were blocked, suggesting that the central nervous system is the primary controller. Indeed these experiments further reinforce the notion of a 'cognitive integrative'(161, 190) or 'central governor' controlling the cardiorespiratory-locomotor response(204). However, what is its relationship to the peripheral nervous system?

Whilst the brain is not an island to itself, it is also clear that signals from working muscle(6, 58, 64, 85, 166) can play a significant role in driving the cardiorespiratory system in exercise. Supported by the observation that exercise rhythm can entrain respiratory rate in a sub-harmonic relationship to limb frequency(19, 191, 192), Coote et al(64) and McCloskey & Mitchell(166) established the neurophysiological basis of the peripheral circuits. Here they showed muscle contraction in the cat elicited by ventral root stimulation underpinned the exercise pressor response, since sectioning the dorsal roots abolished the response. Moreover, group III and IV sensory afferents(166) carried the signal to the posterior hypothalamus(249) and periaqueductal grey in the cat(146). Are these areas the functionally operating circuits in humans during exercise? To test this idea a number of landmark studies in humans have emerged using deep brain stimulation to activate or record from putative areas during exercise itself.

In the late 1990's Thornton and colleagues(241) observed that high frequency stimulation of the sub thalamic (STN) in awake Parkinsonian patients was associated with a small rise in ABP,HR, and facilitated movement. The depolarising block removes the inhibitory break on the locomotor-coupled cardiorespiratory system. As the body prepares for action this inhibitory pathway is probably activated. This idea is supported by Basnayake et al(18) when they adapted the Goodwin et al tendon vibration protocol(106) and recorded LFPS from the STN during constant tension based isometric contraction. They observed that STN activity decreased (removal of inhibitory break) during biceps contraction. During reflex inhibition caused by triceps tendon vibration when more 'central command' was required to maintain constant tension, STN activity was further decreased. This was associated with an increase in cardiorespiratory drive highlighting the inhibitory role of the STN in the basal ganglia circuitry during exercise.

Re-visiting Krogh and Lindhard's classic paper on 'cortical irradiation' driving the anticipatory cardiorespiratory response to exercise, Green and colleagues repeated these experiments and recorded LFPs in several mid brain regions(112). During the anticipatory phase of exercise (with no movement), they found significant firing in the lateral PAG, which was subsequently enhanced during actual exercise. Neural activity then decreased during recovery from exercise, which supported their previous findings showing lateral stimulation of the PAG at rest increased ABP(111). It is well-established that the PAG circuit is a major site associated with cardiovascular and respiratory responses(45, 71, 125, 139, 158, 234) linked to pain and the fight/flight response as previously mentioned. However, the command sequence must originate from higher centres when the decision to exercise is executed. Mid-brain nuclei therefore act as relay stations, although they clearly play a significant role in the cardiorespiratory response since treadmill running and static exercise in rats show an increase in c-fos of the PAG(132, 156). C-fos is an immediate early response gene that has a role in cell proliferation and differentiation and has been shown to increase in

response to external stimuli(117). The importance here is that it implies that the brain area is in some way related to the eternal stimulus. C-fos activity is also increased during treadmill running in other mid brain areas such as the PPN(132), which has recently been shown to be cardiovascularly active during DBS in PD patients(130). It is likely therefore, that these areas also act as integrative areas between top-down and feedback signals.

Further support for the PAG as an integrating area in human physiology for both central and peripheral signals(190) emerges from a study using DBS recording electrodes in patients being treated for neuropathic pain. Here activation of the muscle pressor reflex(3) with electrodes positioned in the PAG provided direct evidence that neural activity from the lateral PAG is increased when BP remains elevated during muscle occlusion following exercise(17). When the cuff was deflated both pressure and nerve activity fell. Of interest, lesioning of the PAG prevents the muscle pressor reflex(253).

One may postulate that, to test whether specific brain areas are significant or indeed obligatory for cardiorespiratory changes associated with exercise, it would be useful to experimentally block such areas during exercise analogous to studies blocking afferent influences from exercising limbs. Whilst we have mentioned two such studies(241, 253), more work needs to be done in this regard. In humans, lesion studies are limited by the need to wait for natural causes (such as stroke) which rarely affect isolated areas but rather affect vascular territories. Another issue is that the exact mechanisms of DBS are not fully elucidated – whilst there is some in depth knowledge of how electrical impulses affect surrounding neurons(52), it is unclear how these effects vary with different frequencies of stimulation (most electrical modelling studies concentrate on the commonly used 130Hz stimulation that is used in movement disorders to simulate a lesion). Furthermore, whilst some human DBS studies have demonstrated activation or inhibition of distant brain areas(98), little is known regarding the effects of DBS on network modulation(147).

Regarding higher cortical command of cardiorespiratory responses, most studies to date have relied on neuroimaging techniques looking at altered vascular activity or metabolic activity such as functional MRI (fMRI) or positron emission tomography (PET). Areas include the ACC, Insula, medial prefrontal areas and thalamus(67, 144, 254-256). Whilst the majority of these areas have not been investigated neurophysiologically in the human, the dorsal ACC is an area under investigation for the treatment of refractory neuropathic pain and a small number of patients have undergone DBS(35). Gillies et al studied a cohort of these patients, measuring LFPs in a central command paradigm and found direct neurophysiological evidence that the dACC is involved in parallel motor preparation and top-down cardiovascular control(99). This is consistent with a number of studies that demonstrate that the ACC is part of central network that drives sympathetic autonomic processing, often in the context of either anticipation (such as cognitive tasks) and the experience of pain(220). Whilst ACC responses involved in anticipation are not exclusively associated with autonomic output(89),Critchley et al have also shown the converse; that the ACC can generate cardiovascular arousal independent of cognitive and motor activity(68)

Using DBS to explore the CAN and other brain areas in relation to autonomic control is dependent on treatment of conditions for which DBS is being used in any case. One such condition is Chronic Cluster Headache (CCH). CCH belongs to a classification of headache disorders known as the *trigeminal autonomic cephalalgias (TAC)*. These are headaches characterised by unilateral head pain

associated with prominent autonomic features. The latter include conjunctival injection, eyelid swelling, ptosis (drooping eyelid), tearing, rhinorrhoea (runny nose), and redness and swelling of the skin on the affected side. The fact that they are unilateral and respect the midline is particularly interesting phenomenologially because it may help to understand the pathosphysiology. For example, there is clear evidence that autonomic activity switches from one side to the other several times per day, and that this 'lateralized ultradian rhythm' is present both at cerebral hemisphere level as well as at the end organ level such as the nasal cycle in which one breathes alternately through one nostril and then the other in approximately four hour cycles(223). In addition, the timing of these alternations can be modulated by 'tricking' the brain such as using 'forced nostril breathing'(224). There is a clear relationship between circadian rhythms and cluster headache. In the 'episodic' form, the headaches tend to cluster at certain times of the year (hence the term 'cluster headaches') and often occur in clusters of 3-4 at a particular time of day or night. Cluster headaches are usually extremely severe and whilst many patients will gain relief from drugs such as the triptans, many are left in extremis. The pain is associated with agitation and can be so severe that the condition has been labelled the 'suicide headache'. The rationale for DBS in CCH (not the episodic form which is generally not treated with DBS) is based on functional imaging studies by May et al(163) in which the posterior hypothalamus was found to be overactive during the attack. Since high frequency DBS is thought to reduce activity of brain regions, Leone et al(155) subsequently applied DBS to this region with impressive results.

The underlying pathophysiology of autonomic changes in the TACs is likely to be related to the trigeminocervical complex that contains afferents from the trigeminal branches innervating the face and side of the cranium (and the dura mater), and the upper cervical nerves. This pathway then projects to higher brain areas. The autonomic features are a combination of increased parasympathetic activity (lacrimation, rhinorrhea, eyelid swelling) and concomitant reduction in other sympathetic functions (ptosis and meiosis). The stimulation of trigeminal afferents in animals and humans can lead to increased cranial autonomic outflow known as the *trigeminal autonomic reflex(164)*. It has been suggested that abnormalities in this reflex underlie the severity of the autonomic changes in CCH(164) and furthermore, that central disinhibition results from activation of the posterior hypothalamus that contains both pro- and antinociceptive peptides(16) (Orexin A and B respectively) and is linked to circadian rhythms. Direct stimulation of the posterior hypothalamus in humans was investigated by Cortelli et al(65) who found increased DBP, total peripheral resistance (TPR) and LF/HF ratio of HRV during head up tilt with stimulation compared to rest. These findings suggest an increase in sympathoexcitability as a result of reducing posterior hypothalamic activity with DBS and fit with some of the authors (unpublished) observations of increasing BP with stimulation. DBS of a neighbouring area, the ventral striatum has also been shown to increase HR and BP in patients undergoing treatment for severe obsessive-compulsive disorder (244). It is likely that stimulation of the ventral striatum (that in some patients may encompass the same target as in Cortelli's study) stimulates the trigemino-hypothalamic tract(2).

Exploring other areas and the future role of DBS research

DBS provides us with the opportunity to explore human brain areas in a way that has only previously been possible using functional imaging techniques, electroencephalography (EEG), or natural lesioning studies. The characteristic of recording LFPs from brain electrodes allows a different information set as changes in electrical activity can be recorded in the microsecond range (c.f. fMRI

over several seconds) and the compound actvitity can be decomposed into individual frequencies to provide rich information on electrical processing in the brain. Whilst magnetoencephalography can record a similar temporal resolution, it cannot reliably record at depth in the brain. The disadvantage of LFPs in humans is that we are limited to areas that we are using for treatment, unlike fMRI that can look at networks in the whole brain. However, another aspect of using DBS is that we can look at the effects of stimulation itself on autonomic and other parameters. This not only provides more information, but also gives insights into potential treatments and paves the way for translation of the research. Another recording technique used in epilepsy diagnosis – stereo EEG (SEEG) – involves the insertion of multiple electrodes (often 15-20) in order to localise an epileptic focus that might be a target for resection(51). Lacuey et al used this opportunity of by stimulating electrodes that are primarily used for recording and found that stimulation of the subcallosal neocortex (Brodmann area 25) induced profound hypotension(153). Similarly, Chouchou et al have investigated the role of the human Insula and shown that insula stimulation can cause tachycardia or bradycardia depending on the site of stimulation(55).

Future research is likely to benefit from the ever-increasing number of conditions that are being treatedwith DBS. Advancement of MRI compatible DBS systems(105) may eventually allow us to perform fMRI on and off stimulation and look at network activity. Improved electrode design such as greater numbers of contacts and devices that record LFPs in chronically implanted patients(127) will allow researchers to relate brain recordings to specific 'real world' situations. Similarly, the use of 'wearables' i.e. devices that can be attached to the subject such as accelerometers, BP and HR monitors in wrist mounted devices will allow accurate measurement of autonomic and other parameters to gauge how well stimulation is working in the longer term, not just in the laboratory. Future studies are therefore likely to combine clinical trials with robust mechanistic data. The former will benefit patients directly and the latter will increase our understanding of how the brain processes autonomic information and influences peripheral cardiovascular control. Advances in basic neuroscience methods such as DTI is already allowing clinicians to 'predict' DBS targets(129), and future studies may include a degree of 'precision medicine(8)' i.e. tailoring the therapy, such as the exact target location, to the individual patient.

Conclusions

DBS has a long history going back several decades. At the time of writing, it is mainly being used for movement disorders, the most common indication being PD. PD, as detailed in this review, is associated with profound autonomic changes that gives us some insight into how stimulating specific brain areas can alter autonomic phenotypes in the context of pathophysiology. In those patients without autonomic failure – either PD or other indications such as pain – DBS has allowed us to look at how modulating the brain affects normal physiology. Many of the brain areas used for DBS have been extensively investigated in animal models such as the PAG and Hypothalamus. When the animal and human data are viewed synergistically, they have advanced our understanding of the neural circuitry underpinning central control of the autonomic nervous system.

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Figure Legends

Figure 1. Brain areas known to be involved in autonomic control. Shaded areas are approximate regions. Note that the insula is in the mesial temporal lobe lateral to the basal ganglia which is not shown and the area therefore appears out of the picture. Midline structures are surrounded by a broken line.

Figure 2. A and B. To perform Deep Brain Stimulation, the target is accurately planned on an MRI scan and custom targeting software (such as Renishaw Neuroinspire® depicted here). **C.** Surgery is performed to insert the electrode using a stereotactic frame. Intraoperative testing may be used in awake patients. **D.** The brain electrodes are connected via a subcutaneous extension wire to an implantable pulse generator placed in a subcutaneous pocket (courtesy of Dr Binith Cheeran, Abbott Neuromodulation).

Figure 3. Looking at the mechanisms of the effect of DBS on autonomic parameters. A microneurographer (inset) can record from the autonomic fibres within the peroneal muscle. Comparing DBS On and Off shows that stimulation of the dorsal subthalamic nucleus increases muscle sympathetic nerve activity and is associated with a small increase in BP. Adapted from Sverrisdottir YB et al 2014.

Figure 4. Study of DBS patients allows a number of investigations to elucidate brain function in the context of cardiorespiratory function. This particular study used subjects with indwelling DBS electrodes in the Pedunculopontine Nucleus (PPN) for the treatment of Parkinson's disease. **A.** Position of electrode contacts studied in a group of patients undergoing PPN stimulation. **B.** Local Field Potentials (LFPs) tell us how the PPN is changing electrically. Here, the patient undergoes head up tilt testing (HUTT)(blue vertical line) and there is a resultant reduction in alpha (8-12Hz) activity in the PPN. **C.** Physiological testing demonstrates that PPN stimulation reduces the postural drop in BP on HUTT. 'On' refers to stimulation 'On' rather than levodopa effects. **D.** DTI analysis demonstrates connections between PPN and other brain areas. Adapted from Hyam JA et al 2019

Figure 5. BP changes resulting from intraoperative stimulation of two different areas of the PAG in a single subject. A. BP reduction resulted from ventral stimulation in the first position studied. B. As the electrode was advanced, stimulation posteriorly in the dorsal PAG resulted in increased BP. C. An axial MRI showing an electrode contact in the left PAG (arrow). D. A schematic sagittal section in the midline to show the electrode position relative to surrounding structures.

Cross references

Autonomic adjustments to exercise in humans

Dysautonomia in Parkinson's disease

Hierarchical organization of autonomic pathways

Integration of central and peripheral regulation of the circulation during exercise: acute and chronic adaptations

Neural control of the Ciculation