Differentiated Baroreflex Modulation of Sympathetic Nerve Activity During Deep Brain Stimulation in Humans

Yrsa B. Sverrisdóttir, Alexander L. Green, Tipu Z. Aziz, Nor Faizal A. Bahuri, Jonathan Hyam, Shanika D. Basnayake, David J. Paterson

Abstract—Targeted electric deep brain stimulation in midbrain nuclei in humans alters cardiovascular parameters, presumably by modulating autonomic and baroreflex function. Baroreflex modulation of sympathetic outflow is crucial for cardiovascular regulation and is hypothesized to occur at 2 distinct brain locations. The aim of this study was to evaluate sympathetic outflow in humans with deep brain stimulating electrodes during ON and OFF stimulation of specific midbrain nuclei known to regulate cardiovascular function. Multiunit muscle sympathetic nerve activity was recorded in 17 patients undergoing deep brain stimulation for treatment of chronic neuropathic pain (n=7) and Parkinson disease (n=10). Sympathetic outflow was recorded during ON and OFF stimulation. Arterial blood pressure, heart rate, and respiratory frequency were monitored during the recording session, and spontaneous vasomotor and cardiac baroreflex sensitivity were assessed. Head-up tilt testing was performed separately in the patients with Parkinson disease postoperatively. Stimulation of the dorsal most part of the subthalamic nucleus and ventrolateral periaqueductal gray resulted in improved vasomotor baroreflex sensitivity, decreased burst frequency and blood pressure, unchanged burst amplitude distribution, and a reduced fall in blood pressure after tilt. Stimulation of the dorsolateral periaqueductal gray resulted in a shift in burst amplitude distribution toward larger amplitudes, decreased spontaneous beat-to-beat blood pressure variability, and unchanged burst frequency, baroreflex sensitivity, and blood pressure. Our results indicate that a differentiated regulation of sympathetic outflow occurs in the subthalamic nucleus and periaqueductal gray. These results may have implications in our understanding of abnormal sympathetic discharge in cardiovascular disease and provide an opportunity for therapeutic targeting. (Hypertension. 2014;63:1000-1010.)

Key Words: baroreflex ■ deep brain stimulation ■ Parkinson disease ■ sympathetic nervous system

The arterial baroreflex regulates cardiovascular homeostasis on a beat-to-beat basis through complex interactions between central and peripheral reflex mechanisms. High sensitivity of the baroreflex reflects healthy cardiovascular function, whereas low sensitivity has been shown to be a negative prognostic indicator associated with increased cardiovascular risk and sudden cardiac death.1,2

Modulation of brain activity in humans has proven a successful therapy for otherwise treatment-resistant disorders. The importance of targeting midbrain structures for pain relief,3 movement disorders,4 and understanding the cardiovascular response to exercise6 is now well documented. Electric stimulation of specific midbrain areas in humans affects heart rate (HR), arterial blood pressure (ABP), and the response of BP to standing depending on the site of stimulation in humans.7,8 Furthermore, these findings also indicate that these structures may be involved and important for regulating human cardiovascular reflex control, by modulating autonomic activity. Direct evidence for their involvement in cardiovascular control has come from animal studies. Specifically, Kabat et al9 showed that periaqueductal gray (PAG) area stimulation in cats can alter BP, later characterized as part of the defense reaction with associated emotional and autonomic responses.10-12 Similarly, Eldridge et al13 demonstrated that stimulation of the midbrain locomotor region which is equivalent to the subthalamic nucleus (STN) in humans drives locomotion and cardiorespiratory responses in decorticate cats, independent of feedback from contracting muscles. These fundamental findings reinforce the role of midbrain circuits in cardiac and vascular control.

Evidence of a differentiated baroreflex modulation of central sympathetic outflow has been reported previously.14 It is suggested to occur at 2 central nervous system locations, one that determines whether or not a burst will occur and another at which the strength of the discharge is determined.15 Although not fully clarified where in the central nervous system this takes place, brain stem connections have been implicated.16 This study aimed to test the hypothesis that midbrain structures affect cardiovascular outcome by modulating baroreflex restraint of central sympathetic outflow at distinct neural sites. To that end, we directly recorded efferent postganglionic sympathetic nerve traffic and cardiovascular parameters in patients.
consecutively undergoing treatment with deep brain stimulating electrodes during ON and OFF stimulation phases. Here, we show that there is a differentiated regulation of sympathetic outflow occurring in the PAG and STN.

Methods

Subjects

Patients undergoing deep brain stimulation (DBS) for treatment of severe Parkinson disease (n=10) and chronic neuropathic pain (n=7) were consecutively recruited for this study.

In the Parkinson’s group, deep brain stimulating electrodes were placed in the subthalamic nuclei (STN; n=6), the globus pallidus internus bilaterally (n=2), the pedunculopontine nuclei (PPN; n=1), and the motor thalamus (n=1). All the patients in this group had idiopathic Parkinson disease. At time of investigation, 3 patients had autonomic dysfunction. One had diminished BP response to orthostatic provocation, and 2 had clinically evident orthostatic hypotension, of which 1 had coexistent supine hypertension and chronic obstructive pulmonary disease, but none had other metabolic or cardiovascular diseases known to disturb autonomic regulation. All patients except PPN were stimulated at 130 Hz between 1.5 and 3.5 V. The PPN was stimulated at 35 Hz and 2.5 V. Time from surgery to time of investigation was 3.3±0.37 months. All DBS electrodes were internalized at the time of investigation.

In the chronic neuropathic pain group, electrodes were placed in the PAG dorsolateral (n=1) and ventrolateral (n=1), the sensory thalamus (n=2), where 1 patient was investigated on 2 separate occasions 2 years apart, and in the anterior cingulate cortex (n=3). Causes of neuropathic pain in this group were stroke (n=3), facial neuralgia (n=2), plexus brachialis injury (n=1), and phantom limb (n=1). At the time of investigation, 4 patients had diseases known to affect autonomic regulation, (hypertension, n=3 and respiratory disorder, n=1). The PAG and sensory thalamus were stimulated between 20 and 50 Hz and 2.5 and 4.5 V. The anterior cingulate cortex was stimulated at 130 Hz between 2.0 and 4.2 V.

Time from DBS electrode implantation and internalization to time of investigation was 3 to 30 months. Pain during ON–OFF stimulation was measured with visual analog scores of pain (scale of 1–100).

This study was performed in accordance with the Declaration of Helsinki. All patients were investigated without withdrawal of ongoing medication (Table 1). The study was approved by the local ethics committee (Oxfordshire Regional Ethics Committee, study No. 05/Q1605/47), and all patients gave written informed consent.

DBS Surgery

Electrodes (Medtronic, Minneapolis, MN) were implanted stereotactically as follows. A Cosman–Roberts–Wells base ring (Radionics, Burlington, MA) was applied to the patient’s head under local anesthetic. A stereotactic computed tomographic scan was obtained and merged to the preoperative magnetic resonance using Renishaw NeuroInspire software (Renishaw, Gloucestershire, United Kingdom). The coordinates thus obtained were used in the Cosman–Roberts–Wells frame, and after suitable skin preparation and sterile technique, 2.7-mm twist drill craniostomies were performed for each electrode. The electrodes were tested clinically and fixed to the skull using a titanium bioplate. The wires were then connected, via extension leads, to an implantable pulse generator placed in a subcutaneous pocket. This second stage of the procedure was either performed at the same operation or after a week of testing with externalized wires.

Our detailed technique regarding specific targets has been described elsewhere.

Data Analysis

The preoperative MRI scan fused with a postoperative computed tomographic scan for each patient was used to determine the electrode location in each nucleus and the values of X (representing the median–lateral [sagittal view]), Y (representing the anterior–posterior [coronal view]), and Z (representing the superior–inferior [axial view]) were calculated in Montreal Neurological Institute space. All coordinates were normalized to the right side for electrode localization, plotting, and pattern identification and are expressed relative to the anterior commissure.

Microneurography

After electrode internalization, direct recordings of multiunit postganglionic sympathetic nerve activity to the muscle vascular bed (MSNA) were obtained with a tungsten microelectrode inserted into a muscle fascicle of the peroneal nerve posterior to the fibular head. Patients were tested with the deep brain stimulator set ON or OFF at random at beginning of recording. Details of the nerve recording technique and criteria for MSNA have been reported previously. A low-impedence reference electrode was inserted subcutaneously a few centimeters away. When a muscle nerve fascicle had been identified, small electrode adjustments were made until a site was found at which spontaneous, pulse-synchronous bursts of neural activity could be recorded. The original nerve signal was amplified with a gain of 50000 and fed through a bandpass filter with a band width of 700 to 2000 Hz and then through an integrating network with a time constant of 0.1 seconds, to obtain a mean voltage display of nerve activity. All nerve recordings were performed with the subjects in the supine position. During the recording, finger ABP was measured noninvasively by the volume-clamp method (Finapres 2300; Ohmeda, Louisville, KY), HR was monitored via ECG-chest electrodes, and respiratory frequency via a strain-gage strapped around the chest/waist. Analog signals of the filtered and mean voltage neurogram together with an ECG, ABP, and respiratory movements were stored on a computer (sampling frequency, 200 Hz). The subjects’ health records and previous laboratory findings were assigned a code and therefore blinded to the examiner.

Analyses of Sympathetic Nerve Activity

A 5-minute resting period during each DBS ON–OFF phase was chosen for analyses. The mean values for systolic and diastolic pressure and cardiac interval were calculated by custom-made computer software, and the respective standard deviation was used as a measure of the variability of pressure and cardiac interval.

Bursts of neural activity were identified by inspection of the mean voltage neurogram, aided by custom-made computer software and quantified by their occurrence over time (bursts/min), expressed as burst frequency (BF) or their incidence in association to HR (bursts/100 heartbeats), expressed as burst incidence (BI). As a measure of the strength of a sympathetic burst, its mean voltage amplitude was also generated by the custom-made computer software. The software calculates the start, maximum, and end point for each individual sympathetic burst separately, leaving measures of burst strength unaffected by shifts in baseline of the neurogram. The amplitude of

### Table 1. Ongoing Medication in the Two Study Groups

<table>
<thead>
<tr>
<th>Medication</th>
<th>PD Group (n=10)</th>
<th>NP Group (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopaminergic medication</td>
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</tr>
<tr>
<td>Antihypertensive treatment</td>
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<td>2</td>
</tr>
<tr>
<td>Antihypotensive treatment</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Respiratory medication</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Opiates</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Antidepressants</td>
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<td>0</td>
</tr>
<tr>
<td>NSAID</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antilipidemia</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

NP group indicates patients treated with deep brain stimulation (DBS) attributable to chronic neuropathic pain; NSAID, nonsteroid anti-inflammatory drugs; and PD group, patients treated with DBS attributable to Parkinson disease.
the largest burst in each analyzed period was set to 100%, and the strength of all other burst amplitudes then expressed in proportion to this value. In this way, a relative burst amplitude spectrum was obtained, and from it a median relative burst amplitude value was extracted and used for statistical analysis.21

Assessment of Individual Baroreflex Diagrams
In this study, the beat-to-beat BP variation was evaluated and related to the corresponding sympathetic burst amplitude to generate a baroreflex sensitivity (BRS) diagram. BRS diagrams for cardiac interval were determined in an analogous way.11 The commonly used method of measuring the relationship between MSNA and BP changes induced by injections of vasoactive drugs, that is, phenylephrine and nitroprusside, was not rendered feasible given the severity of disease in several of the patients in the present study.

Head-Up Tilt Test
On a separate occasion postoperatively, 6 of the 10 patients with severe Parkinson disease and deep brain stimulators (STN=5; PPN=1) successfully underwent a head-up tilt test. Patients were tested in a quiet room on their regular antiparkinsonian medications. A 3-lead electrocardiograph recorded HR. Diastolic (DBP) and systolic BP was recorded noninvasively and continuously using a Portapress plethysmograph on the left upper limb. Patients were first tested with the deep brain stimulator set ON or OFF at random. Patients reclined at 0° on a specially designed tilt table for 10 minutes. Head-up tilt to 80° was then performed within 10 seconds and maintained for 10 minutes. The stimulator was then switched ON or OFF accordingly, and the patient returned to 0°. After a further 10 minutes, head-up tilt to 80° was repeated and maintained for 10 minutes. Tilt table movement was captured using an on-board accelerometer which fed into the data acquisition hardware.

Notch filtering was performed at 50 Hz to remove mains artifact. A decrease in systolic BP >20 mm Hg and DBP >10 mm Hg within 3 minutes of tilting was regarded as orthostatic hypotension.21

Statistics
All patients in this study were viewed as case studies. Linear regression analysis was used to characterize cardiac and vascular BRS diagrams. All calculations of significance testing of correlations and slopes of regression lines were performed with the commercially available statistical program, Statistica by Statsoft. Statistical significance was considered at P<0.05.

Results
The mean contact positions and individual active electrode coordinates are shown in Figure 1.

MSNA and BRS in the Parkinson Disease Group
Motor Thalamus, Globus Pallidus Interna, and PPN
Of the patients with active electrodes in these nuclei, 2 were on antihypotensive medication (amantadine) and 1 was on antihypertensive treatment (ramipril; Table 2).

Stimulation of the motor thalamus, globus pallidus internus, and PPN did not result in any significant changes in MSNA whether expressed as BF, BI, or burst amplitude distribution (median relative burst amplitude). Hemodynamic parameters measured and BRS to the vasculature remained unchanged during all DBS ON–OFF phases of these nuclei.

STN: Dorsal Most Targets
Of the 3 patients in this group, 2 had clinically verified orthostatic hypotension, of which 1 had coexistent supine hypertension and chronic obstructive pulmonary disease (Figure 2A), and 1 had diminished BP response to orthostatic provocation. None were on antihypotensive or antihypertensive treatment at time of investigation, but 1 was on respiratory medication.

DBS ON
BRS to the vasculature increased, showing regression lines with a slope that was significantly different from zero. The increase in BRS resulted in a significant decrease in MSNA BF and BI which was paralleled by reductions in ABP and HR (Figure 2A).

DBS OFF
BRS to the vasculature was lost, with regression slopes not significantly different from zero. The loss of BRS resulted in an increase in MSNA BF and BI which was paralleled by an increased HR and ABP (Figure 2A).

During both DBS ON and OFF stimulation, MSNA burst amplitude distribution (median relative burst amplitude) remained unchanged in all subjects.

STN: Less Dorsal Targets
In this group, 1 patient had untreated hypertension at time of investigation. Bilateral DBS ON–OFF of the more ventral part of the dorsal STN (closer to mid-STN) resulted in unchanged BRS to the vasculature with 1 patient showing significant regression slopes and 2 patients showing nonsignificant slopes during all stimulation phases. The lack of change in BRS to the vasculature was reflected in unchanged MSNA, ABP, and HR during all stimulation phases (Figure 2B).

Cardiac BRS remained nonsignificant during DBS ON–OFF phases in all patients in the Parkinson disease group.

Head-Up Tilt Test
STN: Dorsal Most Targets
The fall in BP after tilt was reduced with STN stimulation ON as compared with stimulation OFF in the 3 patients with electrodes in the dorsal most part of the STN (Figure 3, patients No. 1–3). Mean systolic BP change in this group was −31.76% OFF and −17.6% ON. Mean DBP change was −24.92% OFF and −21.11% ON.

STN: Less Dorsal Targets
Two patients underwent head-up tilt in this group (Figure 3, patients No. 4–5). The patient with significant MSNA/DBP BRS slopes during DBS ON and OFF showed unaltered orthostatic changes after tilt both with stimulation ON and OFF. BP fall with stimulation ON was greater than the OFF state in the other patient, who showed nonsignificant MSNA/DBP BRS slopes during DBS ON and OFF stimulation phases.

Pedunculopontine Nucleus
There was no significant change in BP after tilt in the patient with stimulating electrodes in this nucleus either with stimulation ON or OFF (Figure 3, patient No. 7).

MSNA and BRS in the Chronic Neuropathic Pain Group
Sensory Thalamus and Anterior Cingulate Cortex
Stimulation of the sensory thalamus and anterior cingulate cortex did not result in any significant changes in MSNA
The active electrode coordinates of individual patients (relative to the anterior comissure).

<table>
<thead>
<tr>
<th></th>
<th>STN (gray)</th>
<th>X (mm)</th>
<th>Y (mm)</th>
<th>Z (mm)</th>
<th>PAG</th>
<th>X (mm)</th>
<th>Y (mm)</th>
<th>Z (mm)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>14</td>
<td>-18</td>
<td>-2.5</td>
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<td>-6.5</td>
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<td>-33</td>
<td>-6</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>13</td>
<td>-15</td>
<td>-5.5</td>
<td></td>
<td></td>
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<td>-15</td>
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<td>-4.5</td>
<td></td>
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</tr>
</tbody>
</table>

Figure 1. Mean and individual contact positions that were stimulated in the subthalamic nucleus (STN) and periaqueductal gray (PAG) targets. A to C, STN electrode positions. The gray dot represents the most dorsal/posterior targets (baroreflex responders), and the white dot represents the more ventral targets (baroreflex nonresponders). D to F, PAG electrode positions. Gray shows the dorsolateral (dl) and the white the ventrolateral (vl) PAG targets. The associated table shows the individual (numbers corresponding to patient numbers in Table 2) coordinates of active deep brain stimulation electrode contacts in Montreal Neurological Institute (MNI) space. X represents the median–lateral (sagittal view), Y represents the anterior–posterior (coronal view), and Z represents the superior–inferior (axial view) position in MNI space. All coordinates have been normalized to the right side for electrode localization, plotting, and pattern identification and represent distance from anterior and posterior commissures AC–PC plane.
whether expressed as BF, BI, or burst amplitude distribution (median relative burst amplitude; Table 3). Hemodynamic parameters measured remained unchanged as did MSNA burst amplitude distribution and burst baroreflex latencies during all DBS ON–OFF phases.

A 2-year follow-up of 1 of the patients with electrodes in the sensory thalamus (patient 3a and 3b in Table 3) revealed no change in MSNA BF, incidence, or amplitude distribution during DBS ON and OFF during the 2-year period, showing the high reproducibility of the results. An interesting observation in this patient, with previous coronary artery disease and a cerebral vascular accident, is stimulation of the sensory thalamus abolished arrhythmias in form of extrasystoles evident during DBS OFF. The observation remained during the 2-year follow-up.

### Dorsolateral PAG

**DBS ON**

MSNA burst amplitude distribution changed toward a mesokurtic form, indicating a shift toward a greater number of medium- to high-amplitude bursts than low-amplitude bursts. The shift in burst amplitude distribution was paralleled by a decrease in spontaneous BP variability (DBP variance: 4.1). The changes in burst amplitude distribution were not accompanied by a change in burst latency values.

**DBS OFF**

MSNA BF and BI remained unchanged, whereas burst amplitude distribution took on a leptokurtic form demonstrating a transfer toward a greater number of low-amplitude bursts than medium- to high-amplitude bursts (Figure 4A). The burst amplitude distribution was paralleled by an increase in spontaneous BP variability (DBP variance: 8.6).

BRS to the heart and vasculature remained unchanged during both DBS ON and OFF, showing regression lines with a slope not significantly different from zero. The lack of change in BRS to the vasculature was reflected in unchanged MSNA BF and BI, ABP, and HR (Figure 4A).

### Ventrolateral PAG

**DBS ON**

Vascular BRS increased and MSNA BF and BI decreased, which was paralleled by reductions in ABP and HR. MSNA burst amplitude distribution showed a leptokurtic form, demonstrating a greater number of low-amplitude bursts than medium- to high-amplitude bursts (Figure 4B). Respiratory frequency was 12 breaths/min.

**DBS OFF**

Vascular BRS was lost, and MSNA BF and BI increased, paralleled by an increase in ABP and HR (Figure 4B). Burst amplitude distribution remained leptokurtic, and spontaneous BP variability remained unchanged. The increase in MSNA and ABP during OFF stimulation was related to the sensation of pain (Table 3). Respiratory frequency was 9 breaths/min with intermitted apneas.

Cardiac BRS remained nonsignificant during all DBS ON and OFF phases in all subjects.

### Discussion

Notwithstanding the underlying pathologies of each patient and given the nature of case study reports, we present 2 novel findings. First, we show that stimulation of the most dorsal targets of the STN for treatment of Parkinson disease improves BRS to the vasculature in those with accompanying autonomic dysfunction. Second, stimulation of the dorsal or ventral PAG for treatment of chronic neuropathic pain results in a differentiated sympathetic discharge pattern and hemodynamic response related to different pain relief mechanisms.

### Regulation of the Occurrence and Intensity of a Sympathetic Burst

Frequency and intensity of central sympathetic nerve traffic has been shown to be controlled independently by the arterial baroreflex. 14,16,27 Although it is not known how the differentiated control of sympathetic bursts is brought about, a previous study 15 suggested that the baroreflex modulation of

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**Table 2. Sympathetic and Hemodynamic Characteristics of Individual Patients in the Parkinson Disease Group**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration, y</th>
<th>Target</th>
<th>DOS SBP/DBP, mm Hg</th>
<th>DBS ON</th>
<th>HR</th>
<th>MSNA (BF/BI)</th>
<th>MSNA (MRBA%)</th>
<th>BRS/DBP (r Value)</th>
<th>DBP/DBP, mm Hg</th>
<th>DOS SBP/DBP, mm Hg</th>
<th>DBS OFF</th>
<th>HR</th>
<th>MSNA (BF/BI)</th>
<th>MSNA (MRBA%)</th>
<th>BRS/DBP (r Value)</th>
<th>DBP/DBP, mm Hg</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>STN</td>
<td>118/79*</td>
<td></td>
<td>57*</td>
<td>33/56*</td>
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<td>112/76*</td>
<td>61*</td>
<td>40/66*</td>
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<td>−0.1*</td>
<td>118/79*</td>
<td>61*</td>
<td>40/66*</td>
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<tr>
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<td>42*</td>
<td>25/60*</td>
<td>38</td>
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<td>125/73*</td>
<td>42*</td>
<td>25/60*</td>
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<td>3</td>
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<td>STN</td>
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<td>73*</td>
<td>40/54*</td>
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<td>−0.3*</td>
<td>120/60*</td>
<td>87*</td>
<td>58/66*</td>
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<td>0.3*</td>
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<td>16/19</td>
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<td></td>
<td>72</td>
<td>29/41</td>
<td>56</td>
<td>−0.05</td>
<td>120/80</td>
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<td>27/39</td>
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<td>−0.02</td>
<td>133/72</td>
<td>92</td>
<td>14/15</td>
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BF indicates burst frequency; BI, burst incidence; BRS/DBP, baroreflex sensitivity for diastolic blood pressure; DOS, day of surgery; GP(i), globus pallidus internus; HR, heart rate; MRBA%, median relative burst amplitude; MSNA, muscle sympathetic nerve activity; PPN, pedunculopontine nucleus; SBP/DBP, systolic blood pressure/diastolic blood pressure; STN, subthalamic nucleus; and VIM, motor thalamus.

*Significant intraindividual changes in measured parameters.
Figure 2. A. Mean voltage neurogram of resting muscle sympathetic nerve activity (MSNA), spontaneous blood pressure (BP) recording, and the corresponding baroreflex sensitivity (BRS) diagrams for diastolic BP (DBP) during DBS ON and OFF periods in a patient with coexistent supine hypertension and orthostatic hypotension with bilateral electrodes in the dorsal most part of the subthalamic nucleus (STN). Burst amplitude distribution remained unchanged (median relative burst amplitude [MRBA%], 46 vs 44, respectively).

B. Mean voltage neurogram of resting MSNA, spontaneous BP recording, and the corresponding BRS diagrams for DBP during ON and OFF DBS periods in a patient with bilateral electrodes in the more ventral part of the dorsal STN. Burst amplitude distribution remained unchanged (MRBA%, 39 vs 39, respectively). BF indicates burst frequency; and DBS, deep brain stimulation.
sympathetic outflow occurs at 2 central nervous system locations, one that determines whether or not a burst will occur and another at which the strength of the discharge is determined.

**MSNA and BRS in STN Targets**

Besides the skeletal motor dysfunction in Parkinson disease, cardiovascular motor dysfunction is also a common finding. Disturbed sympathetic nerve traffic and depressed arterial BRS underlie the increased cardiovascular mortality reported in association with the condition. Stimulation of the STN improves the skeletal motor dysfunction in these patients and alters cardiovascular parameters. Although the cardiovascular and autonomic responses are well known in the STN, the dorsal and ventral areas of the nucleus are proposed to serve different functions. Stimulation of the dorsal area, involved in somatosensory functions, produces cardiovascular responses, whereas stimulation of the ventral area produces emotionally related responses, linked to associative-limbic autonomic functions rather than cardiovascular control. Recently, Liu et al demonstrated enhanced autonomic regulation of the HR in patients with STN electrodes. They proposed that the response was attributable to distribution of electric signals to limbic components of the STN or descending sympathetic pathways in the dorsal most part of the STN, the zona incerta. Here, we demonstrate that stimulating targets located in the most dorsal part of the STN is associated with increased baroreflex inhibition of central sympathetic outflow resulting in decreased sympathetic BF, BP, and HR and a reduced postural fall in systolic BP during head-up tilt (Figure 3), which was lost when stimulation was turned off (Figure 2A). The cardiovascular response to head-up tilt in our patients was similar to those studied by

#### Table 3. Sympathetic and Hemodynamic Characteristics of Individual Patients in the Neuropathic Pain Group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Target</th>
<th>DOS SBP/DBP, mmHg</th>
<th>HR</th>
<th>MSNA (BF/BI)</th>
<th>MSNA (MRBA%)</th>
<th>BRS/DBP (r Value)</th>
<th>SBP/DBP, mmHg</th>
<th>DBS ON</th>
<th>HR</th>
<th>MSNA (BF/BI)</th>
<th>MSNA (MRBA%)</th>
<th>BRS/DBP (r Value)</th>
<th>SBP/DBP, mmHg</th>
<th>DBS OFF</th>
<th>HR</th>
<th>MSNA (BF/BI)</th>
<th>MSNA (MRBA%)</th>
<th>BRS/DBP (r Value)</th>
<th>SBP/DBP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>diPAG</td>
<td>120/85</td>
<td>84*</td>
<td>38/63</td>
<td>48*</td>
<td>0.07</td>
<td>148/95</td>
<td></td>
<td></td>
<td>38/66</td>
<td>34*</td>
<td>−0.04</td>
<td>148/116</td>
<td></td>
<td></td>
<td>38/66</td>
<td>34*</td>
<td>−0.04</td>
<td>148/116</td>
</tr>
<tr>
<td>2</td>
<td>vlPAG</td>
<td>133/80</td>
<td>69*</td>
<td>16/25*</td>
<td>37</td>
<td>−0.4*</td>
<td>129/72*</td>
<td></td>
<td></td>
<td>24/29*</td>
<td>39</td>
<td>−0.12*</td>
<td>145/97*</td>
<td></td>
<td></td>
<td>24/29*</td>
<td>39</td>
<td>−0.12*</td>
<td>145/97*</td>
</tr>
<tr>
<td>3a</td>
<td>ST (L)</td>
<td>103/76</td>
<td>54</td>
<td>30/54</td>
<td>34</td>
<td>0.03</td>
<td>107/64</td>
<td></td>
<td></td>
<td>34/58</td>
<td>38</td>
<td>0.05</td>
<td>106/61</td>
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<td></td>
<td>34/58</td>
<td>38</td>
<td>0.05</td>
<td>106/61</td>
</tr>
<tr>
<td>3b</td>
<td>ST (L)</td>
<td>103/76</td>
<td>55</td>
<td>30/54</td>
<td>39</td>
<td>0.03</td>
<td>128/73</td>
<td></td>
<td></td>
<td>34/58</td>
<td>49</td>
<td>0.05</td>
<td>120/73</td>
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<td>34/58</td>
<td>49</td>
<td>0.05</td>
<td>120/73</td>
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<tr>
<td>4</td>
<td>ST (R)</td>
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<td>56/83</td>
<td>49</td>
<td>ns</td>
<td>156/82</td>
<td></td>
<td></td>
<td>52/77</td>
<td>63</td>
<td>ns</td>
<td>155/87</td>
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<td>63</td>
<td>ns</td>
<td>155/87</td>
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<tr>
<td>5</td>
<td>ACC</td>
<td>120/80</td>
<td>62</td>
<td>22/34</td>
<td>38</td>
<td>−0.17</td>
<td>133/77</td>
<td></td>
<td></td>
<td>23/35</td>
<td>37</td>
<td>−0.3</td>
<td>135/80</td>
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<td>23/35</td>
<td>37</td>
<td>−0.3</td>
<td>135/80</td>
</tr>
<tr>
<td>6</td>
<td>ACC</td>
<td>119/79</td>
<td>73</td>
<td>19/26</td>
<td>37</td>
<td>ns</td>
<td>110/69</td>
<td></td>
<td></td>
<td>18/23</td>
<td>36</td>
<td>ns</td>
<td>112/72</td>
<td></td>
<td></td>
<td>18/23</td>
<td>36</td>
<td>ns</td>
<td>112/72</td>
</tr>
<tr>
<td>7</td>
<td>ACC</td>
<td>159/96</td>
<td>65</td>
<td>32/49</td>
<td>34</td>
<td>−0.17</td>
<td>179/101</td>
<td></td>
<td></td>
<td>32/50</td>
<td>35</td>
<td>0.3</td>
<td>176/99</td>
<td></td>
<td></td>
<td>32/50</td>
<td>35</td>
<td>0.3</td>
<td>176/99</td>
</tr>
</tbody>
</table>

ACC indicates anterior cingulate cortex (bilateral); BF, burst frequency; BI, burst incidence; BRS/DBP, baroreflex sensitivity for diastolic blood pressure; diPAG, dorsolateral periaqueductal gray; DOS, day of surgery; HR, heart rate (beats/min); MRBA%, median relative burst amplitude; MSNA, muscle sympathetic nerve activity; ns, not significant; SBP/DBP, systolic blood pressure/diastolic blood pressure; ST, sensory thalamus unilateral, left (L) and right (R); and vlPAG, ventrolateral periaqueductal gray.

*Significant intraindividual changes in measured parameters.
Figure 4. A. Mean voltage neurogram of resting muscle sympathetic nerve activity (MSNA) and the corresponding spontaneous blood pressure (BP) recording in a patient with a unilateral electrode in the dorsolateral area of the periaqueductal gray (PAG) during DBS OFF and ON periods. The arrows in the histograms indicate the median relative burst amplitude (MRBA%) for each histogram, respectively. Baroreflex sensitivity remained nonsignificant ($r = -0.04$, $P = 0.3$ and $r = 0.07$, $P = 0.4$, respectively).

B. Mean voltage neurogram of resting MSNA, spontaneous BP recording, and the corresponding baroreflex sensitivity diagrams for diastolic BP (DBP) during DBS ON and OFF periods in a patient with a unilateral electrode in the ventrolateral PAG area. Burst amplitude distribution remained unchanged (MRBA%, 36 vs 38, respectively). BF indicates burst frequency; and DBS, deep brain stimulation.
Stemper et al. Moreover, stimulating targets more ventrally in the dorsal STN had no autonomic or cardiovascular effects during rest (Figure 2B) or head-up tilt (Figure 3). Stimulation of either the dorsal most or less dorsal STN targets had no effect on sympathetic burst amplitude distribution.

**MSNA and BRS in PAG Targets**

The PAG is a complex midbrain region involved in regulating bodily as well as behavioral functions and is routinely used to treat chronic neuropathic pain. Electric stimulation of this area has been shown to have cardiovascular effects in humans. Activation of the ventrolateral column produces a reduction in cardiovascular activity, whereas activation of the dorsolateral column is associated with an increased cardiovascular activation. The dorsolateral, lateral, and ventrolateral columns of the PAG have distinct reciprocal connections with autonomic centers of the lower brain stem and hypothalamus that differentially regulate activity in neurons of the peripheral autonomic pathways. Our results show that stimulation of the dorsolateral and ventrolateral columns of the PAG for treatment of chronic neuropathic pain results in a differentiated sympathetic discharge pattern and hemodynamic response related to the underlying mechanism for pain relief.

**Dorsal PAG**

The distinctive nerve firing pattern of a shift in burst amplitude distribution toward larger amplitudes, without a concomitant increase in occurrence of sympathetic bursts, as seen in our patient during stimulation of the dorsolateral PAG, has previously been reported in conditions associated with anxiety and stress. In a study by Wilkinson et al., sympathetic outflow in patients during a panic attack revealed an increase in burst amplitude in the absence of an alteration in BF indicating either increased recruitment of silent fibers or an elevation in the firing rate of individual vasoconstrictor neurons. Furthermore, in normal healthy males, an arousal stimulus (mental stress) is shown to cause an increase in the amplitude of a sympathetic burst but not its frequency. A shift toward a greater number of high burst amplitudes and hence number of active fibers firing together, as observed in our patients during stimulation of the dorsal PAG, is in line with these findings.

An active coping response (fight and flight) occurs when an individual encounters a threatening stimulus that may be harmful or cause pain. This defense pattern is represented in the dorsomedial and dorsolateral PAG and is classically associated with endogenous nonopioid analgesia, increased ABP, and HR. Although recent evidence in humans suggests that it may in fact be opioid mediated, our results show that in the absence of an external threat, the nerve firing pattern and cardiovascular response to electric stimulation of the dorsolateral PAG for treatment of chronic pain resembles that of arousal and defense pattern, and perhaps this may explain the pain relief.

**Ventral PAG**

A passive coping response (quiescence) is a natural reaction to serious injury and chronic pain and is represented in the ventrolateral PAG and manifest as decreased BP, HR, and (classically) endogenous opioid-sensitive analgesia. Our results show that stimulation of the ventrolateral PAG results in decreased sympathetic BF, ABP, and HR. An interaction between BP and pain regulatory systems is indicated by an association between increased BP and decreased pain sensitivity in humans and animals. Although not fully understood, it is suggested that the baroreflex control of cardiovascular regulation may mediate antinociception in hypertensive conditions.

Stimulation of the nucleus tractus solitarius, the first synapse of the baroreceptor afferents, elicits antinociception through either direct or indirect efferent projections to the PAG and structures as the rostral ventrolateral medulla. Our results of increased baroreflex inhibition of central sympathetic outflow during electric stimulation of the ventrolateral PAG are in line with a hypothesized baroreceptor-mediated antinociception through inhibition of the endogenous opioid system.

**Limitations of the Study**

Needless to say, a study of such complexity as the present one is not without limitations. First, although DBS is becoming more common as a form of therapy for otherwise treatment-resistant disorders, the general pool of patients undergoing DBS is not large. The number of those willing and rendered eligible to participate in research is therefore relatively small, and each patient is unique and valuable. Of the total of patients recruited for this study, 9 did not meet the strict criteria for a successful sympathetic nerve recording during both ON and OFF DBS phases and were therefore excluded. The study group thus consists of 17 patients, 10 with Parkinson disease and 7 with chronic neuropathic pain, which in perspective is not a small number in such a complex patient group.

Second, because of the extensive clinical investigations before surgery, we were unable to record sympathetic outflow preoperatively and can therefore not compare the effects of medication per se with ON/OFF DBS on autonomic and cardiovascular function. Although medication may have been changed after surgery, all patients were investigated without withdrawal of ongoing medication in the present study and medication was not varied between ON and OFF DBS phases. Levodopa treatment has been shown to induce several negative effects on autonomic function by lowering BP and HR and therefore worsen orthostatic hypotension. A reduction in levodopa intake attributable to STN stimulation therefore improves autonomic function in patients with Parkinson disease as well as enhances the effect of STN-DBS on cognitive function. Although differences in dopaminergic medication state could have influenced our results, this is unlikely given that the entire experiment took <1 hour, during which time variance of dopaminergic state would be only modest. In addition, the order of stimulation was randomized. Therefore, any changes in autonomic and cardiovascular responses in this study were regarded as effects of electrode stimulation.

**Perspectives**

Although we only report case studies, this study strongly suggests that differentiated baroreflex modulation of central sympathetic outflow occurs in 2 distinct midbrain nuclei, the STN and the PAG. The results may have wide implications as they increase our understanding of pathological sympathetic outflow associated with vascular disease. Diminished sympathetic BRS is associated with increased cardiovascular...
morbidity and mortality in general and more specifically, in Parkinson disease, to produce orthostatic hypotension. Because of the debilitating burden of orthostatic hypotension, it is important to identify a target that can aid BP regulation and improve quality of life for these patients. Furthermore, we suggest that the pain relief associated with stimulation of the dorsal and ventral PAG is accompanied with a differentiated sympathetic and hemodynamic response. Together, these results suggest there is an important coupling between pain and cardiovascular autonomic integration.

Whether DBS can be used to counter some of the harmful cardiovascular effects of dysautonomia remains to be established. Nevertheless, we suggest a 2 a priori sites that might be therapeutic targets for future clinical investigations.

Acknowledgments
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This work was funded by The British Heart Foundation (BHF) grant No. PG/11/3/28555. In addition, some of the authors (A.L. Green, Y.B. Sverrisdóttir, T.Z. Aziz, D.J. Paterson) are supported by The NIHR Biomedical Research Centre (Oxford).

Disclosures
None.

References


What Is New?
- This study is the first of its kind to relate activation of targeted midbrain nuclei to directly recorded efferent postganglionic sympathetic nerve traffic in humans with deep brain stimulating electrodes.

What Is Relevant?
- We show that differentiated regulation of central sympathetic nerve traffic occurs in the subthalamic nucleus and periaqueductal gray. The results are highly relevant for our understanding of pathophysiological sympathetic nerve activity.
- Being able to identify a midbrain target that can improve sympathetic baroreflex sensitivity and blood pressure regulation in patients with Parkinson disease may be therapeutically beneficial.

Novelty and Significance

Deep brain stimulation of targeted central neurocircuitries on efferent sympathetic nerve traffic provides direct evidence for a differentiated control of frequency and intensity of sympathetic bursts that resides in distinct midbrain nuclei. The results may provide an opportunity for therapeutic targeting in case of cardiovascular dysautonomia.
Differentiated Baroreflex Modulation of Sympathetic Nerve Activity During Deep Brain Stimulation in Humans

Yrsa B. Sverrisdóttir, Alexander L. Green, Tipu Z. Aziz, Nor Faizal A. Bahuri, Jonathan Hyam, Shanika D. Basnayake and David J. Paterson

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