Modulation of Muscle Tone and Sympathovagal Balance in Cervical Dystonia Using Percutaneous Stimulation of the Auricular Vagus Nerve

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Abstract: Primary cervical dystonia is characterized by abnormal, involuntary, and sustained contractions of cervical muscles. Current ways of treatment focus on alleviating symptomatic muscle activity. Besides pharmacological treatment, in severe cases patients may receive neuromodulative intervention such as deep brain stimulation. However, these (highly invasive) methods have some major drawbacks. For the first time, percutaneous auricular vagus nerve stimulation (pVNS) was applied in a single case of primary cervical dystonia. Auricular vagus nerve stimulation was already shown to modulate the (autonomic) sympathovagal balance of the body and proved to be an effective treatment in acute and chronic pain, epilepsy, as well as major depression. pVNS effects on cervical dystonia may be hypothesized to rely upon: (i) the alteration of sensory input to the brain, which affects structures involved in the genesis of motoric and nonmotoric dystonic symptoms; and (ii) the alteration of the sympathovagal balance with a sustained impact on involuntary movement control, pain, quality of sleep, and general well-being. The presented data provide experimental evidence that pVNS may be a new alternative and minimally invasive treatment in primary cervical dystonia. One female patient (age 50 years) suffering from therapy refractory cervical dystonia was treated with pVNS over 20 months. Significant improvement in muscle pain, dystonic symptoms, and autonomic regulation as well as a subjective improvement in motility, sleep, and mood were achieved. A subjective improvement in pain recorded by visual analog scale ratings (0–10) was observed from 5.42 to 3.92 (medians). Significant reduction of muscle tone was also achieved in sitting and standing positions of the patient. Habituation to stimulation leading to reduced stimulation efficiency was observed and counteracted by varying stimulation patterns. Experimental evidence is provided for significantly varied sympathovagal modulation in response to pVNS during sleep, assessed via heart rate variability (HRV). Time domain measures like the root mean square of successive normal to normal heart beat intervals, representing parasympathetic (vagal) activity, increased from 37.8 to 67.6 ms (medians). Spectral domain measures of HRV also show a shift to a more pronounced parasympathetic activity. Key Words: Auricular vagus nerve—Neuromodulation—Sympathovagal balance—Cervical dystonia—Heart rate variability—Electromyography.

Cervical dystonia (CD) is the most common form in adult-onset dystonia (1). CD represents a severe illness affecting the motor function, with detrimental impact on general well-being and on social life. The disease can be characterized by focalized abnormal, involuntary, and spasmodic or repetitive contractions of cervical muscles (2). Induced muscle activation and resulting abnormal postures are often associated with impaired voluntary movements and severe pain. There is evidence that CD is accompanied with nonmotor symptoms, like impaired sensorimotor integration as well as impaired neuropsychiatric, cognitive, and sleep regulation (3). Symptoms may vary over time and are usually modulated by posture, or in general additional sensory input. A sensory trick (geste antagoniste), like touching the forehead
or the chin, may temporarily alleviate symptoms in up to 70% of patients with CD (3). However, the pathophysiology of primary dystonia is only partly understood and may involve pathological processes widely spread over functional brain networks (4).

Current ways of treatment focus on alleviating symptomatic and painful muscle activities by affecting their contractility. Pharmacological inhibition is used with pain and muscle relaxant medication or botulinum toxin injections to block synaptic transmission at the neuromuscular junction (5). Medication most often alleviates symptoms only slightly and botulinum toxin may lead to significantly reduced motility as unfavorable side effects. In therapy refractory cases, denervation of muscles or neuromodulative interventions, that is, deep brain stimulation (DBS) of basal ganglia structures, comprise further options of treatment, both being highly invasive and holding appropriate risks (5,6). However, DBS in CD is routinely applied bilaterally in the internal pallidal segment (GPi) and the subthalamic nucleus. Mean reduction rates of dystonic symptoms in response to GPi-DBS assessed via various rating scales, like the Toronto Western Spasmodic Torticollis Rating Scale, range to about 60–80% at 15–24 months follow-up (7,8). Reduction in pain was also reported. Motoric improvements are typically delayed by several months after DBS onset, but may be maintained even over 10 years of therapy (9). However, as with pharmacological treatment, DBS is a symptomatic treatment with no effect on the progression of the disease and a typical recurrence of symptoms after turning off the stimulation (6).

Possible new interventions avoiding the aforementioned drawbacks of current treatment should consider: (i) the impairment of sensorimotor integration in dystonia; and (ii) a possible link of dystonic symptoms to pathological alterations in sympathovagal balance of the autonomous nervous system. Based on these considerations, percutaneous auricular vagus nerve stimulation (pVNS) may be a new asset in treating CD (10). pVNS can modulate afferent inputs to the brain affecting both the brain regions involved in the genesis of motoric and nonmotoric dystonic symptoms (3,11–13), as well as the sympathovagal balance (14–16). The normalization of the sympathovagal balance may lead to a sustained impact on muscle tone and involuntary movement control, pain, quality of sleep, and general well-being (14,17–20).

Concerning the sympathovagal balance, it should be noted that most physiological processes are involuntarily controlled via the autonomic nervous system, composed out of sympathetic and parasympathetic branches (21). While activation of the sympathetic nervous system is associated with increased heart rate, blood pressure, or muscle tone, activation of parasympathetic branches leads to opposing effects such as decreased heart rate and cardiac contractility (21). In a healthy subject these two subsystems are in balance, which (i) maintains individual and optimal values of physiological parameters, for example, muscle tone or blood pressure, and (ii) allows the body to appropriately react to external or internal perturbations, for example, exogenous stressors (21,22). Pain, stress, inflammation or other pathological conditions can affect this balance and lead to changed values of physiological parameters and changed modulation of these parameters due to these disturbances.

The vagus nerve is often concerned as the main nerve of the parasympathetic nervous system (23). Cervical branches of the vagus nerve mediate afferent and efferent (motoric and parasympathetic) innervation of pharynx, larynx, heart, lungs, and viscer al organs (23). Additionally, auricular branches of the vagus nerve mediate an afferent innervation of the auricle (24,25).

Due to the functional organization of the vagus nerve and its projections to various brain regions, a number of physiological processes are affected by modulating its afferent components (23,26,27). For instance, invasive cervical vagus nerve stimulation (cVNS) is an established treatment for therapy refractory epilepsy, major depression, and more recently congestive heart failure (26,28–30). Furthermore, stimulation of the auricular vagus nerve was already shown to be a possible treatment for acute and chronic pain, vascular diseases, and therapy refractory epilepsy (17,18,31–33).

pVNS can be considered as a minimally invasive and easy to establish method of neuromodulative intervention (34). In particular, the concha, antihelix, and tragus region of the auricle are stimulated, which are innervated to a large extent by afferent Aβ- and Aδ-fibers of the vagus nerve (24,35). This solely afferent innervation avoids side effects in pVNS, which are likely to occur in cVNS (e.g., hoarseness, cough, pain, or dyspnea) due to the mixed afferent and efferent character of the cervical vagus nerve (36). Auricular vagus nerve stimulation was already shown to modulate activity in brain regions involved in autonomic regulation, alertness, mood, or motor control (i.e., the nucleus of the solitary tract, nucleus accumbens, locus ceruleus, amygdala, thalamus, or prefrontal cortex) (11–13). Thus, brain regions
involved in autonomous regulation of involuntary movements relevant to CD, for example, in controlling posture or gaze, may favorably be affected by pVNS (see Discussion). In addition, improved autonomic control and increased parasympathetic power in response to pVNS were already observed by our group using heart rate variability (HRV) analysis (14,15,18).

In this article we propose a new methodological approach for the treatment of CD using multipunctual pVNS as already shortly introduced in our contributions (34,37). In short, the electrical stimulation aims at modulation of the sensory input to brain structures involved in the genesis of dystonic symptoms as well as at modulation of autonomous, sympathovagal regulation.

In the following, stimulation paradigms are detailed. Preliminary data on therapeutic outcome are presented for one patient with severe cervical dystonia. Continuously recorded pain ratings during therapy show a significant decrease in the subjective pain perception. Surface electromyography measurements of the affected cervical muscles were performed to validate pVNS effects and to control the success of therapy. Monitored muscle tone reveals information on strength and pattern of involuntary muscle contraction. Long-term electrocardiography holter monitoring was performed, which allows for the validation of pVNS-induced changes in autonomous sympathovagal regulation, based on HRV analysis. HRV and muscle tone indicate a significant improvement of dystonic symptoms and autonomous regulation in response to pVNS. Habituation to stimulation leading to reduced stimulation efficiency was observed and counteracted by continuous readjustment of applied stimulation patterns. Possible signal transduction pathways in the brain and future implications of pVNS in terms of CD therapy are discussed.

**MATERIALS AND METHODS**

**Modulation of sympathovagal balance**

Multipunctual pVNS is mediated via multiple needle electrodes, for example, four electrodes with one acting as the reference (34). Electrodes are inserted into vagally innervated regions of the auricle; see Fig. 1 (part I) and Fig. 2. Conductive rings attached to stimulation wires establish a connection between the stimulation electrodes and the stimulation device.

**FIG. 1.** pVNS. (I) Multipunctual pVNS. (II) Suggested afferent signal transduction pathway (sensory input). (III) Induced effects on sympathovagal balance. (IV) Balanced modulation of physiological parameters like muscle tone or heart rate. An imbalanced autonomous system (point A) may not only lead to an overshooting reaction to a perturbation, for example, an exogeneous stressor, but also to a reduced ability to counteract such stressor.

**FIG. 2.** Application of stimulation electrodes at four sensory innervated regions of the right auricle.
Modulation of afferent vagal nerve branches in the auricle can be expected to elicit changes in activation patterns of specific brain structures (Fig. 1, part II), especially of the nucleus of the solitary tract in the brainstem (11–13). Stimulated projections to parasympathetic nuclei as well as to higher brain regions lead to feedback-controlled modulation (Fig. 1, part III) of various bodily networks (20), for example, involuntary control of heart rate or cervical muscle tone, and finally may lead to a shift in the sympathovagal balance (Fig. 1, part IV).

In a healthy and balanced bodily system (external and internal) perturbations like stress or pain can be appropriately counteracted to maintain the body’s homeostasis, whereas an imbalanced autonomous system (Fig. 1, point A) does not allow the body to react properly to these drivers (21,22). In the latter case, the body is forced to maintain an over- or underexpressed autonomous state.

Stimulation setup

Stimulation patterns for pVNS comprise biphasic voltage impulses with programmable amplitude \(A\), 0–2 V), pulse width \(\text{pw}\), 500–1000 μs), frequency \(f_p\), 1–100 Hz), and on/off cycle (110/15 min). Burst stimulation is possible with \(n = 2–250\) pulses/burst and burst frequencies \(f_b\) of 1–2 Hz (Fig. 3).

Stimulation was continuously applied over 20 months. At each visit (every 1–2 weeks), the site of the stimulation was changed to the opposite ear. To account for and eliminate habituation/adaptation processes observed during treatment (see Discussion), stimulation patterns were frequently adapted to achieve a continuous alleviation of symptoms. Amplitude of stimulation was adjusted to produce a nonpainful but distinct tingling sensation at the auricle, with the aim of modulating thick Aβ-fibers of the auricular vagus nerve (35).

Patient data

pVNS was applied on one female patient (age 50 years) with a 4.5-year history in refractory CD. No further diseases which may have caused or which influence dystonic symptoms could be identified during clinical evaluation. The disease was characterized by bilateral sustained and periodic contractions of cervical muscles, leading to a high impairment in motility and general well-being. Dystonia was accompanied by muscle pain, severe problems with sleep, depressed mood, and lack of appetite. Symptoms slightly differed in lying, standing, and sitting positions. Touching the chin as a sensory trick (geste antagoniste) led to a short but slight alleviation of symptoms in standing and sitting positions. The patient was refractory to pain, anticonvulsive, antiepileptic as well as muscle relaxant medication, and did not tolerate botulinum toxin injections at the affected muscles, that is, the right and left superior portions of the trapezius muscle.

Data assessment and analysis

Pain perception was assessed as one therapeutic outcome measure using 24 h visual analog scale (VAS) ratings, ranging from 0 (no pain) to 10 (intolerable pain). The patient was advised to record one value every 2 h for each day. Although VAS is an important measure to evaluate the subjective state of the patient, it does not necessarily represent changes in actual muscle tone, pattern of muscle activation, and autonomous state, which may all be important parameters for tracking effects of pVNS. The surface electromyography (sEMG) signals from the left and right trapezius muscles were recorded at each follow-up visit. sEMG data were used to objectively observe and control for differences in involuntary muscle activation due to varying stimulation patterns of pVNS.

sEMG data were recorded at a sample frequency of 1 kHz using an MP36 acquisition system (BIOPAC Systems Inc., Goleta, CA, USA). The raw signal was low pass filtered at 500 Hz. For data analysis, the filtered sEMG signals were rectified and averaged in a moving window with a length of 200 samples. Analyses were performed on representative data segments of 20-s length.

Additionally, at two follow-up visits in month 6 and month 18 of treatment, 24 h holter monitoring (electrocardiography, ECG) using a medilog AR12 holter monitor and software medilog DARWIN v. 1.13.5 (Schiller Handels-GesmbH, Austria) was performed to observe possible changes in sympathovagal balance as derived from HRV (37,38). Two
8.5-h long segments of ECG data during sleep (22:30–7:00) were used for mutual comparison. That is, data recorded during daytime were not appropriate for comparison of autonomous regulation because neither physical activity nor other confounding boundary conditions were controlled at the two monitoring periods.

HRV was analyzed using standardized time domain and spectral domain measures of normal to normal heart beat intervals, that is, the time intervals between two successive R-peaks of QRS-complexes in ECG (37,38). Inspected time measures of HRV are the standard deviation of all heart beat intervals (\(SDNN\)); the root mean square of successive differences of intervals (\(RMSSD\)); the percentage of intervals (\(pNN50\)), which differ by more than 50 ms; and the standard deviation (\(SDANN\)) of 5-min averaged heart beat intervals. In addition, these parameters were calculated over a moving window of 5-min length with an overlap of 50% (\(SDNN_{5\text{min}}\), \(RMSSD_{5\text{min}}\), and \(pNN50_{5\text{min}}\)).

Spectral domain measures of HRV are the total power (\(TP\), 0.0033–0.4 Hz), the high frequency power (\(HF\), 0.15–0.4 Hz), as well as the ratios very low frequency power to \(TP\) (\(VLF/TP\), 0.0033–0.04 Hz), low frequency power to \(TP\) (\(LF/TP\), 0.04–0.15 Hz), high frequency power to \(TP\) (\(HF/TP\), 0.15–0.4 Hz), and low to high frequency power (\(LF/HF\)).

Statistical analysis
To test for significant differences in sample medians of VAS, rectified sEMG, and HRV data at various time instances during therapy, non-parametric Wilcoxon rank sum tests were applied (significance level \(\alpha = 5\%\)). Statistical analysis was performed using MATLAB R2012b (The MathWorks Inc., Natick, MA, USA).

All boxplots in this article give median values as lines in the boxes, which range from the 25th percentile \(q_1\) to the 75th percentile \(q_3\). Whiskers extend to the most extreme data points \(x\) not considered as outliers (\(x < q_3 + 1.5 * (q_3 - q_1)\) and \(x > q_3 - 1.5 * (q_3 - q_1)\)). Outliers are not indicated.

RESULTS

Pain perception
Continuous recording of subjective data by VAS (see Fig. 4a) revealed a decrease over the first 3 months (M) of treatment with a first significant difference at M2 (4.83, median) to M0 (5.42). The
patient reported a slight relief in dystonic symptoms and a slight increase in motility.

M3 to M5 show again slightly higher and rather stable VAS values between 5.08 and 5.25 (medians), although dystonic muscle activity was reduced during this period (see below). pVNS was continuously readjusted due to occurrence of habituation/adaptation processes caused by a constant stimulation pattern, leading to reduced stimulation efficiency (see Discussion). In the end of M6, the situation of dystonic symptoms, pain, and general well-being worsened significantly due to increased problems with nocturnal sleep accompanied by a decompensating stress disorder, which finally led to hospitalization of the patient for 1 month (Fig. 4a, see point I). pVNS was continued during this period under permanent control of sEMG and stimulation parameters.

Normalization was achieved again in M8 with a further reduction in pain perception during the following months (M8–M12, see Fig. 4a). An overall minimum in VAS was reached at M12 (3.5, median). In the following, pain situation worsened again but resided rather stable after M12, when the patient resumed her professional work. In addition, motility, sleep, mood, general well-being, and appetite continuously improved during treatment.

Figure 4b shows typical courses of VAS for 1 day at M1 of treatment (A) and at M18 of treatment (B). An obvious change in pain perception over the day can be observed, with still high values of pain at M18 due to physical activity (working time from 8:00 to 14:00 in Fig. 4b, see point B) but also a fast and favorable reduction in pain during subsequent relaxation. At the time instance A in Fig. 4b, no physical activity was possible due to severe dystonic symptoms; in addition, the pain perception continuously increased over the day.

Muscle activity

Due to the described subjective relief in dystonic symptoms and a palpable reduction in muscle tone until M2, it was decided to continue treatment via pVNS under continuous (objective) sEMG monitoring. Figure 5 summarizes time courses and the corresponding statistical data for rectified sEMG signals of the left and right trapezius muscles, measured in supine position.

Figure 5a shows a continuous and significant decrease in muscle tone from M3 to M18 of both the left and right muscles by 96.87% (from 67 to 2 μV, medians) and 96.07% (from 31 to 1 μV), respectively. Furthermore, the variation in muscle tone continuously decreased over time, which indicates changes in the involuntary activation patterns of the muscle. An initial asymmetric condition in the activity between the left and the right-sided muscle diminished due to the discussed significant reduction in the effective muscle tone.

Figure 5b depicts discussed trends in the muscle activation patterns based on the rectified sEMG data. The muscle activation pattern apparently changed
from high, phasic contractions to a more tonic activation of muscle fibers, with a reduction in (over-shooting) contraction strength. Full remission of involuntary muscle contractions was achieved.

Similar but less pronounced changes in the muscle activation strength were observed in standing (Fig. 6) and sitting positions (Fig. 7). A significant decrease in muscle tone was achieved in standing position from M6 to M15 of both the left and right muscles by 53.57% (from 28 to 13 μV, medians) and 80.77% (from 26 to 5 μV), respectively. In sitting, the reduction for the left and right muscle amounts to 42.86% (from 14 to 8 μV) and 75% (from 16 to 4 μV), respectively. Although the monitored muscle tone could not be reduced to zero, a complete symptom remission was observed in selected positions of the head. One such position was, for instance, tilting the head slightly to the lower right.

Concerning short-term effects of pVNS (in the range of seconds), Fig. 8 shows an example of the rectified sEMG data from the left and right muscles in the course of the adjustment of stimulation parameters. The length of stimulation bursts $n$ (see Fig. 3) was slightly changed by ±2 pulses/burst. Pulse width ($pw$) and frequencies ($f_p$, $f_b$) remained constant. Amplitude ($A$) was kept constant to maintain a tingling sensation at the stimulation points. Already this slight modification of $n$ led to an immediate change in the pattern of the involuntary muscle activation. A consistent and reproducible decrease in the contraction frequency of about 65% was achieved in this case.

### Autonomic nervous system function

There is evidence for a beneficial change in total HRV and the derived sympathovagal balance at sleep in response to pVNS (19). Tables 1 and 2 summarize time and spectral domain measures of HRV for holter monitoring data at M6 and M18 of treat-

#### TABLE 1. Time domain measures of HRV for 8.5 h holter monitoring during sleep (22:30–07:00) at month 6 (M6) and month 18 (M18) of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>M6</th>
<th>M18</th>
<th>Percental change</th>
</tr>
</thead>
<tbody>
<tr>
<td>$SDNN$</td>
<td>ms</td>
<td>54.6</td>
<td>81</td>
<td>+48.4%</td>
</tr>
<tr>
<td>$SDANN$</td>
<td>ms</td>
<td>46</td>
<td>68.75</td>
<td>+50.9%</td>
</tr>
<tr>
<td>$RMSSD$</td>
<td>ms</td>
<td>30.3</td>
<td>50.5</td>
<td>+66.2%</td>
</tr>
<tr>
<td>$pNN50$</td>
<td>%</td>
<td>16.66</td>
<td>24.5</td>
<td>+47.5%</td>
</tr>
</tbody>
</table>

Percental changes related to M6 indicated in brackets.
An increase in SDNN and TP of more than 100% and 200%, respectively, which both stand for the total HRV, was observed (38,39). Besides this, the time domain measures RMSSD and pNN50, as well as the spectral domain measure HF/TP increased by 25–190%, all of them representing parasympathetic activity. In contrast, the ratio LF/TP increased only slightly, whereas this ratio represents both parasympathetic and sympathetic activity. Additionally, there was a 50% decrease in log (LF/HF), indicating a clear shift of the sympathovagal balance toward parasympathetic activity.

This shift is also confirmed by changes in 5-min values of time and spectral measures. Figure 9 illustrates significant increases of $SDNN_{5\text{min}}$, $pNN50_{5\text{min}}$, and $RMSSD_{5\text{min}}$, as well as a significant decrease of heart rate $HR_{5\text{min}}$ from M6 to M18 during sleep. The time course of $TP_{5\text{min}}$ during sleep in Fig. 10 indicates changes in the autonomous regulation at M18 (Fig. 10b) and a weak regulation level at M6 (except in one 100-min segment around 02:20 where the patient was probably awake but remained in bed, Fig. 10a). The corresponding course of $HF_{5\text{min}}$ indicates an increased parasympathetic activity during the night at M18 as compared with M6. Also, the ratio log (HF/LF) provides experimental evidence for dominating parasympathetic activity at M18 as related to M6.

### TABLE 2. Spectral domain measures of HRV for 8.5 h holter monitoring during sleep (22:30–07:00), at month 6 (M6) and month 18 (M18) of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>M6</th>
<th>M18</th>
<th>Percental change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$TP$</td>
<td>ms²</td>
<td>527.8</td>
<td>1,721</td>
<td>+226.1%</td>
<td>*</td>
</tr>
<tr>
<td>$VLF/TP$</td>
<td>%</td>
<td>42.8</td>
<td>35.2</td>
<td>−17.8%</td>
<td>*</td>
</tr>
<tr>
<td>$LF/TP$</td>
<td>%</td>
<td>31.9</td>
<td>32.6</td>
<td>+2.2%</td>
<td>*</td>
</tr>
<tr>
<td>$HF/TP$</td>
<td>%</td>
<td>21.8</td>
<td>27.4</td>
<td>+25.7%</td>
<td>*</td>
</tr>
<tr>
<td>log (LF/HF)</td>
<td></td>
<td>1</td>
<td>0.2</td>
<td>−50%</td>
<td>*</td>
</tr>
</tbody>
</table>

Percental changes related to M6 indicated in brackets. Presented values represent medians of 5-min data segments with 50% overlap of data segments.

**FIG. 9.** Boxplots for time domain measures of HRV and of heart rate for 8.5 h holter monitoring during sleep (22:30–07:00), at month 6 (M6) and month 18 (M18) of treatment. Plots represent the distribution of parameters calculated from 5-min data segments with 50% overlap of data segments. *$p < 0.01$ to M6.

**FIG. 10.** Time courses of spectral domain measures of HRV for 8.5 hours holter monitoring during sleep (22:30–07:00) (a) at month 6 (M6) and (b) at month 18 (M18) of treatment. Presented data represent parameters calculated from 5-min data segments with 50% overlap of data segments. Shaded areas in log (LF/HF) show dominating parasympathetic activity.
DISCUSSION

A new methodological approach for the potential treatment of CD using multipunctual pVNS was proposed. Experimental data validate favorable changes of pain perception, muscle tone, and autonomous, sympathovagal regulation in one severe case of CD treated with pVNS. Sustained remission of involuntary muscle contractions was achieved in selected postures, which indicates a favorable nonsymptomatic treatment of CD. Based on the presented results, pVNS may be a new alternative, easily applicable, and minimally invasive treatment in primary CD and possibly other movement disorders like tremor or Parkinson’s disease.

In general, muscle activity showed a highly variable behavior during the observation period, dependent on posture, physical activity, site of stimulation, and stimulation pattern (even at the initial onset of stimulation pattern). Small variations in burst length or pulse width of stimulation patterns partially led to immediate changes in muscle tone and its activation pattern. This may indicate a direct interaction of pVNS with functional brain networks involved in motor control, as illustrated in Fig. 11 (40).

Possible signal transduction pathways comprise the following:

a Afferent signals in response to pVNS are forwarded via the jugular ganglion to the two sensory brainstem nuclei of the vagus nerve, that is, the nucleus of the solitary tract and the spinal nucleus of the trigeminal nerve (13, 23). Possible projections to the ambiguous nucleus may establish a direct feedback to cervical muscles by modulating the accessory nerve (41), which innervates the trapezius and the sternocleidomastoid muscle (Fig. 11, part I).

b Afferent signals in response to pVNS are forwarded via the brainstem (reticular formation [FR] and parabrachial nucleus) to cortico-striatal-pallidal-thalamic-cortical (CSPTC), cerebellum, and midbrain structures (Fig. 11, part II). Like in DBS for CD therapy, which targets the internal pallidal segment and the subthalamic nucleus (highlighted in Fig. 11) (6), the complex control loops therein are modulated (12). Finally, pyramidal (gyrus praecentralis) and extrapyramidal (CSPTC, midbrain, FR) efferents are sent to the muscles via the accessory nerve and the cervical plexus, as a potential effect of pVNS.

The above reported strong initial reactions to slight changes in stimulation patterns (e.g., burst length) may additionally indicate a shifted sympathovagal balance and thus an overshooting reaction of the body to an artificial stressor like the electrical stimulation.

Habituation to stimulation pattern was also observed, that is, therapeutic effect on muscle activity decreased over time if the same stimulation pattern was employed over long periods (days or weeks). Interestingly, this adaptation effect diminished at month 8 of treatment resulting in a fixed stimulation pattern which still yielded a continuous improvement in motor control. Thus, therapeutic effects seem to induce neural plasticity in the brain, which is reported to be overexpressed in some dystonia patients (42). This is also supported
by the fact that therapeutic effects persisted even when pVNS stimulation had been turned off for 1–2 days (longer periods of off-stimulation were not tested so far). In contrast to DBS, this may indicate a favorable nonsymptomatic treatment for CD.

Analysis of HRV data revealed a significantly improved autonomous regulation during sleep at month 18 compared with month 6 of treatment. Impairment in sleep typically correlates with disease severity in CD (3). pVNS was already shown to have a favorable effect on sleep efficiency and REM sleep in insomniacs (19), which may have positively influenced therapeutic outcome.

However, definite conclusions on these observations are not possible based on the presented single case of CD without active control of confounding factors, such as medication, physical activity, environment, or psychosocial attitude throughout the reported period of therapy. Other patients may react in a completely different way, as the patient-to-patient variability in neuromodulative interventions is known to be high (43).

No continuous data were assessed on stimulation-induced changes in autonomic regulation. However, there are indications that sympathovagal balance is modulated by changes in the stimulation pattern, which may be an important factor in future studies.

There may be changes in pVNS effects due to varying stimulation amplitudes, as higher amplitudes would not only recruit Aβ-fibers but also Aδ-fibers in the auricle (35). Those may project in different portions of brainstem nuclei. However, in this study stimulation amplitude was adjusted to produce a tingling (but not painful) sensation at the stimulation region, thus we can assume activation of Aβ-fibers only.

Future studies will focus on validation of observed effects in more patients suffering from CD and other forms of dystonia like blepharospasm or writers’ cramp. These studies should allow more insight in the actual pVNS effects while avoiding confounding factors.

In order to improve stimulation effects, biofeedback-controlled stimulation will be established in the future, as already shortly introduced in Kampusch et al. and Kaniusas et al. (34,44). Muscle tone and HRV were shown to properly represent therapeutic outcome in this case of CD, and may also be used in future studies as objective physiological markers to control pVNS therapy. Flexible and adaptable closed-loop stimulation systems offer the possibility to optimize stimulation patterns with respect to individual patients/diseases. It may also allow for a fast identification of (non-)responders, which is hardly possible today. Furthermore, biofeedback may provide better understanding of the complex relationships between stimulation patterns, recorded biosignals, and therapeutic effects.

**Conflict of Interest:** Dr. J.C. Széles holds patents for the applied method of percutaneous auricular vagus nerve stimulation.

**REFERENCES**