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Selective Unilateral Autonomic Activation: Implications for Psychiatry

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Focus Points

• Selective unilateral autonomic activation occurs by unilateral forced nostril breathing, stimulation of the autonomic reflex point on the fifth intercostal space, and vagus nerve stimulation.
• Selective unilateral autonomic activation has important effects on the endogenous lateralized ultradian rhythms of the autonomic and central nervous systems.
• Selective autonomic activation may play an important role in the future for treating a broad range of psychiatric disorders and other health issues.

Abstract

Research advances have led to three methods for selectively activating one half of the autonomic nervous system in humans. The first method is an ancient yogic technique called unilateral forced nostril breathing (UFNB) that employs forced breathing through only one nostril while closing off the other. The second method works by stimulation of an autonomic reflex point on the fifth intercostal space near the axilla. The most recent method employs unilateral vagus nerve stimulation (VNS) via the mid-inferior cervical branch and requires surgical implantation of a wire and pacemaker. UFNB is non-invasive and seems to selectively activate the ipsilateral branch of the sympathetic nervous system with a possible compensation effect leading to contralateral VNS. UFNB and VNS have been employed to treat psychiatric disorders. While UFNB has been studied for its potential effects on the endogenous ultradian rhythms of the autonomic and central nervous system, and their tightly coupled correlates, VNS has yet to be studied in this regard. This article reviews these three methods and discusses their similarities, putative mechanisms, their studied effects on the endogenous autonomic nervous system and central nervous system rhythms, and their implications for the treatment of psychiatric disorders.

Introduction

The Laterality and Dynamics of the Autonomic Nervous System and Its Role in the Regulation of Psychophysiological States

The autonomic nervous system (ANS) is divided into two divisions called the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). Most organs, including the cerebral cortex, are innervated by fibers from both divisions that have opposing effects. The left and right branches of the SNS and PNS each independently innervate the two sides of the body with the vast majority of fibers not crossing over in the cat, rat, and monkey.[1] In addition, the autonomic innervation of the cerebral cortex in the rat occurs primarily via four major hypothalamic projections; the tuberal lateral hypothalamic neurons, the posterior lateral hypothalamic area and supramammillary nucleus, and the fields of Forel, which all show innervation of only the ipsilateral hemisphere, while the fourth area, the tuberomammilary nucleus, innervates both hemispheres approximately equally.[2,3]

The SNS helps prepare for increased levels of activity and the fight or flight response, which includes an increase in heart rate, blood pressure, cardiac output, a diversion of blood flow from the skin and splanchnic vessels to those supplying skeletal muscle, increased pupil size, bronchiolar dilation, contraction of sphincters, and metabolic changes utilizing fat and glycogen.[4-8] In contrast, the influences of the PNS lead to rest, conservation, and restoration of energy and, thus, to a reduction in heart rate (HR), blood pressure, and a facilitation of digestive processes and the elimination of waste products.[8-11]

The ANS is viewed as the "housekeeping" nervous system and it is regulated primarily by the hypothalamus.[4-7,9-13] A unique feature of the ANS, although usually overlooked, is that of the lateralized ultradian rhythms where one branch of the SNS dominates one side of the body, and one branch of the PNS dominates on the opposite side, and then the two systems switch dominance on the two sides.[14-16] For example, if the SNS dominates on the right homolateral half, the PNS will dominate on the left homolateral half, followed by a period with PNS dominance on the right and SNS dominance on the left, thus defining the lateralized ultradian rhythms of the ANS that exhibit with a periodicity in the "hourly" range.[14,15,17-19] This natural hypothalamic-mediated endogenous phenomenon leads to lateralized rhythms of the ANS and the respective innervated organs and structures, which include the cerebral hemispheres.[14,19,20] The nasal cycle is a unique marker for the lateralized rhythms of autonomic function throughout the periphery and it exhibits as an ultradian rhythm with greater airflow in one turbinate, followed by a reversal in airflow dominance.[14,17,19,21-25] Studies have shown that the nasal cycle is tightly coupled to an ultradian rhythm of alternating cerebral hemispheric activity that exhibits both during waking (periodicity ranging from 25–340 minutes with power dominating in the lower-frequency bands and with spectral periods observed in five primary windows at 220–340, 170–215, 115–145, 70–100, and 40–65 minutes)[16,19,26,27] and sleep (periodicity ranging from 25–300 minutes with spectral periods in four primary windows at 280–300, 75–125, 55–70, and 25–50 minutes bins, with power dominating in the 75–125 minutes bin).[16,28,29] Studies have also shown that this lateralized ultradian ANS-central nervous system (CNS) rhythm is also tightly coupled to the ultradian rhythms of the neuroendocrine, cardiovascular, and fuel-regulatory hormone (insulin) systems.[26,27] In addition, it has been shown that catecholamine secretion throughout the periphery alternates in dominance on the two sides of the body when measured under strict resting conditions with sampling through near equivalent antecubital veins in the two arms, and that this left-right pattern of secretion is also tightly coupled to the nasal cycle.[30] These multivariate studies have led to a new view for understanding autonomic and CNS activities and for defining psychophysiological states as regulated and integrated by the hypothalamus, and how the nasal cycle can be a marker for psychophysiological states.[16,19,26-29] This new view of psychophysiological states is a more comprehensive view of Kleitman's Basic Rest-Activity Cycle (BRAC)[31-33] hypothesis proposed in the 1960s that was based on the observations of how rapid eye movement and non-rapid eye movement sleep were coupled to ultradian variations in physiological activity. However, Kleitman's work, and that of others,[34] did not integrate the observations on the lateralized activities of the ANS and CNS that now add a spatial dimension to the temporal BRAC hypothesis. It has also been proposed that the nasal cycle is a marker for psychophysiological states, where right-nostril dominance marks the activity phase of the BRAC and left-nostril dominance marks the rest phase.[14,15,19,20,26-29]

Selective Unilateral Activation of the Left and Right Stellate Ganglion and Vagus Nerves: *Effects on the Heart*

With a dynamic view of autonomic, CNS, and related ultradian phenomenon, it may be possible to have a better understanding for the therapeutic potential of UFNB, vagus nerve stimulation (VNS), and activation of the autonomic reflex point on the fifth intercostal space. The ANS is usually thought of mostly as an efferent fiber system. However, the vagus is a mixed nerve and ~80% of the fibers are actually afferent sensory fibers carrying information to the brain from the head, neck, thorax, and abdomen.[35] This afferent fiber system is what makes VNS a useful therapeutic tool. The influences of the left and right vagus nerves are not identical and VNS studies have empirically led to the selective use of the left cervical (mid-inferior region) branch for prolonged and intermittent stimulation. Studies have shown that stimulation of the right branch can lead to increased cardiac instability.[36]

Levy and Martin[37] reviewed studies on the autonomic innervation and control of the heart. They discuss the lateral differences for both the SNS and PNS. There is considerable right-left asymmetry in the distribution of the sympathetic fibers to the heart.[38,39] In dog studies, Levy and colleagues[38] found that stimulation of the right stellate ganglion can increase HR by 85 beats/minutes, while the effects of left-sided stimulation produce a much smaller increase, and that right-sided stimulation can increase left ventricular systolic pressure by 50 mmHg, while left-sided stimulation increases left ventricular systolic pressure >50 mmHg. They conclude that right-sided stellate ganglion stimulation has greater chronotropic effects while the left produces greater inotropic effects; right stellate ganglion stimulation decreases systolic duration and left-sided stimulation increases mean arterial pressure. Thus, the right sympathetic trunk has relatively greater effect on HR and the left has relatively greater effect on left ventricular function.

The right vagus has a greater cardiac deceleratory effect compared to the left vagus,[40] and right vagus transection causes a greater cardiac acceleration than left transection, suggesting that the right vagus exerts greater restraint on the sino-atrial node compared to the left vagus.[41] Also the heart period is more prolonged when a stimulus is given to the right vagus compared with the left.[40] Henry states: "The left vagus nerve carries most of the parasympathetic fibers that less densely innervate the ventricles, and the right vagus nerve carries most of the parasympathetic fibers that more densely innervate the cardiac atria. Therefore, vagal anatomy favors left (over right) vagus stimulation to avoid cardiac effects."[36] While the unilateral autonomic stimulation effects on the heart are well known, the potential unilateral autonomic stimulation effects on other organs and systems are not so thoroughly studied.

Selective Unilateral Autonomic Activation by UFNB

The ancient yogic technique of UFNB has now been studied in Western laboratories for more than 25 years.[16,42,43] The CNS rhythm of alternating cerebral hemispheric activity and its coupled physiological and psychological correlates are in part the basis for the use and putative effects of UFNB.[14-16,43] Yogis believed that UFNB has effects not only on the brain but throughout the periphery,[16,42,43] and that UFNB selectively stimulates the contralateral cerebral hemisphere and the ipsilateral branch of the sympathetic nervous system.

The first example of using UFNB to selectively stimulate the contralateral hemisphere was demonstrated using electroencephalography (EEG) in young healthy naïve subjects.[44-46] This study involved a continuous measurement of EEG activity in the two cerebral hemispheres using a variety of homologous electrode sites to compare left and right power. Subjects were asked to force breathe through the more congested nostril for 11–20 minutes followed by one, two, or more periods alternating sides with each phase of the experiment.[46] Results showed that UFNB increased EEG power in the contralateral hemisphere regardless of the phase of the nasal cycle. The authors concluded "These results suggest the possibility of a non-invasive approach in the treatment of states of psychopathology where lateralized cerebral dysfunction have been shown to occur."[46]

One study[47] suggests that EEG activity generated by nasal (versus oral) breathing is produced by a neural mechanism in the superior nasal meatus. This activating effect could also be produced by air insufflation into the upper nasal cavity without inflating the lung. Local anesthesia of the nasal mucosal membrane suppressed the cortical effects of airflow stimulation. The contralateral increase in relatively greater EEG power as a marker of greater or lesser mental activity was controversial.[46] The yogic postulate states that UFNB activates the contralateral hemisphere and thus increases cognitive performance in the contralateral hemisphere. One study[48] showed under resting conditions that right-nasal dominance is coupled to relatively greater verbal performance (left brain activity), and left nasal dominance was coupled to relatively greater spatial skills (right brain activity). Two later studies[49,50] using 30 minutes of UFNB with naïve subjects showed that right-UFNB (R-UFNB) increased left hemispheric cognitive performance and that left-UFNB (L-UFNB) increased right hemispheric performance. A more recent study[51] compared R-UFNB, L-UFNB, alternate nostril breathing, and breath awareness as a control for effects on a letter-cancellation left hemispheric task in 20 male volunteers for 30 minutes. Twenty subjects were tested before and after all four interventions on four successive days with variations in the order of the intervention. "The letter cancellation task scores were significantly improved (ie, there were fewer errors following right and alternate nostril breathing). The improved performance may be related to the enhancement of contralateral hemisphere function found with selective nostril breathing."[51] A pilot study[52] using whole-head 148 channel magnetoencephalography explored the effects of left and right UFNB at one breath per minute for 31 minutes and showed similar patterns of contralateral activation and that these same contralateral effects were observed with different frequency bands.[16,43]

Three other groups also studied the effects of UFNB on cognitive performance or mood.[53-55] One study[53] of UFNB on cognitive performance showed a mixed pattern of hemispheric activation with males appearing to have an ipsilateral increase in performance, but "unilateral breathing influences female performance contralaterally, but only on the spatial task." These results were obtained after only 5 minutes of UFNB. In contrast to the results of past studies they state "These differences within and between sexes may exist because unilateral nostril breathing differently activates the two hemispheres and thereby facilitates performance or because attempts of the brain to control the nasal cycle unilaterally interfere with performance." However, an attempt to replicate that study exactly found no nostril-to-condition related performance for either males or females with a 5 minutes exercise period using identical psychological tasks but different subjects.[54]

Klein and colleagues[48] found similar nostril dominance and hemisphere (contralateral) relations for both sexes during rest. It is not likely that the autonomic circuitry differs between sexes. In addition, another study found that UFNB through the dominant nostril also led to greater cognitive performance in the contralateral hemisphere.[55] However, this study did not investigate the UFNB effects in the non-dominant congested nostril. In sum, it may be concluded that the results of these studies are in part dependent on the true lateralized nature of the cognitive tests employed, the breathing times and efforts, and keeping the nostril blocked during the final testing period to help maximize effects.

It appears that nasal airflow may stimulate sympathetic dominance in the homolateral (ipsilateral) body-brain half. A mechanistic principle supporting the effects of UFNB is that this technique produces ipsilateral cortical vasoconstriction (via increased sympathetic tone) and thus reduced blood flow and cortical activity in the ipsilateral brain hemisphere. It has been suggested that increased parasympathetic activation occurs simultaneously in the contralateral hemisphere to compensate for this sympathetic activation, thus helping to maintain adequate cerebral perfusion in total brain.[42] Two clinical trials[56,57] have employed the use of a specific L-UFNB pattern for the treatment of obsessive-compulsive (OCD) with substantial and significant clinical reductions in obsessions and compulsions when measured with the Yale-Brown Obsessive-Compulsive Scale, along with significant reductions in other psychological symptoms using other scales and reductions and elimination of medications.

When considering the peripheral effects of UFNB, the earliest Western scientific study to demonstrate a normal half-sided reaction in autonomic function was that of the relationship of the nose and lung.[58-61] There is a unilateral nasal-pulmonary reflex mechanism which is clearly elicited when there is a forced inhalation through one nostril that has been shown to produce a significant increase in inflation in the homolateral lung. The lung is one organ where sympathetic influences lead to vasodilation rather than vasoconstriction, which then leads to greater blood flow and inflation. Samzelius-Lejdstrom[59] studied 182 individuals and showed that the movements of one thoracal half were much more inflated compared to the contralateral lung in 94% of subjects. She also reported that in cases of tuberculosis where there is primarily a lateralized deficit, there is a simultaneous pathological phenomenon of the homolateral nasal and thoracal halves. One group[62] studied rabbits under experimental conditions and showed that if coal dust was inhaled through one nasal opening, it was deposited in much larger quantities in the homolateral lung. Various studies led by Backon[63-65] have demonstrated the effects of UFNB on several autonomic-dependent phenomena. Backon[63] showed how R-UFNB significantly increased blood glucose levels and how L-UFNB lowered it, and that R-UFNB reduced involuntary eye blink rates and that L-UFNB increased eye blink rates.[64] Backon and colleagues[65] also showed how R-UFNB leads to an average and significant decrease of 23% in intraocular pressure and that L-UFNB increases it by an average but non-significant value of 4.5%. Others have also found that R-UFNB reduced intraocular pressure, but L-UFNB failed to increase it significantly.[66,67] A 1951 review shows how some bilateral structures (eg, kidneys) are regulated with differential resting and activity patterns.[18] A recent study shows how ultradian rhythms can exhibit in the differential blood flow patterns of the two adrenals.[68] And differential autonomic effects on singly represented organs, for example with the heart, lead to ultradian rhythms of cardiovascular activity, as expressed in HR[26,69] and blood pressure.[26] Shannahoff-Khalsa and Kennedy[70] conducted three experiments using impedance cardiography to monitor the beat-to-beat effects of UFNB on the heart. Two experiments employed a respiratory rate of 6 BPM and one experiment employed a rapid rate (2–3 breaths/second) of shallow respiration, employing a yogic technique called “breath of fire” or “kapalabhatti”. These studies all showed that R-UFNB increases HR compared to L-UFNB, which lowers HR. They also showed that stroke volume and end diastolic volume are higher with L-UFNB at 6 BPM. These stimulation effects parallel those described above with the stellate ganglion in dogs, where stimulation of the right stellate ganglion leads to a greater increase in HR compared to stimulation of the left stellate ganglion.[37,38] Another study showed that L-UFNB significantly reduced HR in the subjects that were initially right nostril dominant, but failed to in those who were initially left nostril dominant, and also failed to show any effects of R-UFNB in subjects who were either initially left or right nostril dominant.[71] In yet another study, it was found that R-UFNB increased and L-UFNB decreased systolic and diastolic blood pressure, but only in women with no differential effects found in men.[72]

In addition, R-UFNB, L-UFNB, and alternate nostril breathing (inhaling through the left nostril and exhaling through the right followed by inhaling through the right and exhaling through the left with a continuous alternating sequence) have been compared for their possible effects on metabolism as measured by oxygen consumption.[73] The effects of having “ 27 respiratory cycles, repeated four times a day for 1 month” shows that R-UFNB produced a 37% increase in baseline oxygen consumption, and L-UFNB produced a 24% increase, and alternate nostril breathing increased baseline values by 18%. These researchers also found that L-UFNB led to an increase in volar galvanic skin resistance, interpreted as a reduction in sympathetic activity supplying the sweat glands. In another study, they found that a one time 45-minute practice of R-UFNB increased oxygen consumption by 17%, increased systolic blood pressure by 9.4 mmHg, and decreased digital pulse volume by 45.7%.[74] These results, and the relevant understanding of the autonomic innervation of the heart, help to explain the findings of an open clinical trial using alternate nostril breathing as an effective therapy for treating angina pectoris.[75]

Stimulation of the Autonomic Reflex Point on the Fifth Intercostal Space

Yogis had also learned that lateral recumbency induces ipsilateral nasal congestion and contralateral decongestion, and that by applying pressure to the fifth intercostal space at the axilla, it is possible to affect changes in the nasal cycle and mental states. Novice practitioners were taught to lean on the "yoga danda," a crutch-like device for altering the nasal cycle and cerebral rhythm. The first western reports of such postural effects on the nasal cycle were in the original papers on the nasal cycle,[17,21,24] and then later in classic papers on sweat reflexes and body surface pressures where ipsilateral nasal airflow resistance is produced by application of pressure to the chest wall,[76-78] and with postural effects of pressure in the shoulder region and tested specifically in the axilla.[79]

While yogis had learned to mimic the lateral recumbent effects while remaining upright in either a standing or sitting position, this ability to induce changes while vertical was not reported until 1970.[79] Rao and Potdar[79] studied ancient yogic texts and became aware of the use of the "yoga danda." They were aware that it was used "for correcting right or left nasal airflow."They observed how the pressure in the axilla could induce changes that lead to decongestion in the contralateral nostril. In one set of experiments,

"While the subjects maintained the lateral horizontal posture of the body, the tissue around the shoulder and arm were freed of the squeezing effect. To accomplish this, the subjects were placed in the lateral posture on two tables separated in such a manner that body weight was borne on their temporal region, lateral abdomen, and lateral part of thigh and leg. The lower neck region, shoulder, and hand were free of any weight or pressure. No increase in flow resistance through the down side of the nose was found after 10 minutes in this position."[79]

They believed that the effect is likely autonomic and solely the result of pressure on the surface near the shoulder in the axillary region, and that the neural pathways involved were autonomic.

Later, two leading otolaryngologists,[80-83] well trained in modern methods of measuring nasal airflow, performed a series of complex experiments to study the effects of lateral recumbency on nasal airflow in great detail. In a set of experiments they compared 45 seconds versus 12 minutes of lateral recumbency; the effect upon nasal resistance of progressively lengthening the periods of lateral recumbency; short periods of lateral recumbency immediately after the reciprocating phase of the nasal cycle; the magnitude of nasal resistance changes after rotation of hips or of whole body; determined if pressure, warmth, or touch, are effective in inducing ipsilateral nasal congestion and contralateral decongestion; and whether these effects could be blocked by injection of a local anesthetic or by topical nasal decongestants.[81] They found that in the 45 seconds versus 12 minutes study, that "the resistive changes reversed within approximately 60 seconds of the termination of lateral recumbency, but after 12 minutes they persisted for 15 minutes or more." They conclude here that "there are two nasal responses to lateral recumbency, a "transient" and a "sustained," and that the difference is due to temporal summation."[81] When observing effects of progressive lengthening, they found "that with progressively longer periods of lateral recumbency the nasal response increased in magnitude, endured for longer, and a sustained phase reversal was produced." Also, when checking short periods of lateral recumbency immediately after the reciprocating phase of the nasal cycle, they found that ipsilateral nasal congestion is usually adopted, but also that the nasal cycle continues after long lateral recumbent periods, often after 2 hours. They found that both the transient changes and the sustained reversals are prevented by local anesthetic blockade of the cervical sympathetic ganglion. They concluded that the efferent pathway for both responses is via the sympathetic fibers to the erectile tissue of the nasal mucosa and that the receptors are located deep in the subcutaneous tissue but superficial to thoracic viscera. In addition, they did not find that warmth alone could elicit changes in nasal patency, and that pressures to the head, arms or legs were not effective, nor to the abdomen or lower dorsum. They concluded that the pressure-sensitive zones are located in the ventral, dorsal and lateral aspects of the pelvic and pectoral girdles and thoracic wall. They also state that "This topographical distribution is strikingly similar to that which induces contralateral sweating in response to localized pressure: the "hemi-hydrotic reflex." Therefore there is a possibility that these responses share a common afferent pathway."[81] They also mention that deviated septums and unilateral fixed nasal obstruction in some patients may well have pathological significance in sleep.

Selective Unilateral Autonomic Activation by Vagal Nerve Stimulation

The dynamic view of ANS-CNS interactions may help us to better understand the therapeutic potential of VNS and its potential risks. VNS has been shown to be an important therapeutic tool for the treatment of pharmacoresistent epilepsy and it has shown to yield an average decline in seizure frequency of 25% to 30% when patients (N=313) are treated with a high stimulation rate (30 Hz, 30 seconds on/5 minutes off; 500 µsecond pulse width) compared with a low stimulation rate (1 Hz, 30 seconds on/90–180 minutes off; 130 µsecond pulse width), which yields only a 6% to 15% reduction in seizure frequency.[84-86] VNS is well tolerated, however, it is not a substitute for antiepileptic medication.[87] Long-term VNS therapy for epilepsy patients resulted in a 35% reduction in seizure frequency at 1 year, 44.3% at 2 years, and 44.1% at 3 years. The proportion of patients with sustained seizure frequency reductions of ≥50% was 23% at 3 months, 36.8% at 1 year, 43.2% at 2 years, and 42.7% at 3 years. It seems that the acute 3-month response increases up to the second year of treatment, after which response rates tend to plateau.[84,88,89] Also, the positive response during acute treatment suggests that this can be maintained for longer periods.[88] It is claimed that long-term treatment was well tolerated, with continuation rates of 96.7% at 1 year, 84.7% at 2 years, and 72.1% at 3 years.[84] VNS is also claimed to be effective in children 3–18 years of age with median reductions in seizure frequency at 3, 6, 12, and 18 months of 23%, 31%, 34%, and 42%, respectively.[90]

VNS has also been studied with treatment resistant depression patients. To date, two trials have been published. The first[91,92] was an uncontrolled pilot study (N=60) looking at the acute effects in 10 weeks (N=60), and the second[93] was a larger, double-masked, sham-controlled, 10-week trial (N=235). Fifty-nine of the 60 patients in the pilot completed the study, and 18 (30.5%) were considered responders ($\geq$50% reduction in baseline 28-item Hamilton Rating Scale for Depression [HAM-D_{28}]), and 9 (15.3%) remitted (HAM-D_{28} total score $\leq$10). Improvement was gradual, with a mean of 48.1 days until the response was significant. None of the patients withdrew due to adverse events. The larger study compared VNS with sham treatment with either unipolar depression patients or bipolar patients in the depressed-phase. There were 112 patients in the treatment group (high/stronger stimulation rates) and 110 in the sham group (low/weaker stimulation rates).[94] The device was activated (single-blinded) after a 2-week post-implantation recovery period and stimulation parameters were adjusted during the first 3 weeks post-activation and fixed for the remaining 8 weeks of the trial. While the device was well tolerated, there was no short-term demonstration of efficacy in the response rates ($\geq$50% reduction in baseline HAM-D_{28}), with the active group showing 15.2% and the sham group a 10.0% improvement. However, when long-term rates of efficacy were calculated with the 59 patients who completed the short-term pilot study,[91,92] and met response criteria as early responders (3 months) or as late responders (1 year) and followed for 2 years,[95] the 3-month response rates of 30.5% increased to 44.1% at 1 year and were 42.4% at 2 years.[95] Also, when maintenance of response was considered, 55.6% of early responders and 78.6% of late responders continued as responders at the 2-year mark.[96] When rates of remission were considered in a subset of 30 patients (remission is defined as <10 on the HAM-D_{28}), there was a significant increase from 17% at 3 months (five of 30 patients) to 29% at 1 year (eight of 28 patients).[97] Similar sustained results in the larger study[94] were observed with the follow up of 205 patients where the treatment group showed a response rate for remission of 27.2% and the sham group showed 15.8%. One might conclude that VNS therapy holds some promise for treatment refractory depression. However, the mechanisms of the effects are not completely understood.

Since VNS causes brain effects in regions also believed to regulate anxiety, and there were major reductions in anxiety in the first depression study, a multi-site open trial in treatment-resistant anxiety disorder patients was launched involving 30 anxiety disorder patients with a primary diagnosis of either OCD, posttraumatic stress disorder, or panic disorder.[98] No results are reported to date for this trial, however, others have also discussed the potential utility of VNS for OCD.[99,100] VNS has also been suggested as a therapy for treating obesity, pain, Alzheimer's disease, and other neuropsychiatic disorders.[98]

However, VNS requires general anesthesia that may also include other surgical procedures after initial placement. Therefore, recent attention has been directed towards potential perioperative complications post-implantation, and other anesthetic considerations during initial placement and anesthetic management issues for patients with a pre-existing VNS device.[87]

The stimulation parameters of VNS (high/stronger stimulation rates vs low/weaker stimulation rates) are important factors and they are discussed in depth in the efficacious treatment of epilepsy and depression.[36,90,98,101] The concepts of pulsatility and structured stimulation patterns are also important parameters with some of the more advanced UFNB techniques. Examples of the possible complexity of UFNB patterns that requires altering rates of pulsatile stimulation are described in detail.[15,16,42,43]

Conclusion

In addition to the effects of selective unilateral autonomic activation by UFNB on the brain, heart, and other organs and systems innervated by the ANS, and in the treatment of OCD,[56,57] the more modern method of VNS has shown a benefit in the treatment of pharmacoresistent epilepsy,[102] major depression[91,103] and may eventually show potential with OCD and other anxiety disorders.[99] "It is concluded that although the precise mechanism of action of VNS is still unknown, the search for the mechanism has the potential to lend new insight into the neuropathology of depression."[104]

One might conclude that the effects of VNS may also be mediated by similar mechanisms to those of UFNB—a generalized differential activation of one half of the ANS. In fact, yogis refer to the vagus as the "mind nerve" (Yogi Bhajan, personal communication, November 1978). It may be that VNS has a relatively simple unilateral influence that may be useful for a variety of psychological and physiological disorders. Two researchers comment on VNS "the latency of response in patients with epilepsy or treatment-resistant depression suggests that VNS therapy may trigger a process of neural adaptation rather than directly targeting the specific pathophysiological deficits of the disorder."[105]

When considering additional applications for UFNB and VNS, it should be noted that the nasal cycle, handedness, and eye dominance have recently been compared in 37 children with autism and 20 controls.[106] Twenty-seven boys with autism (mean age: 9.04 years) and 10 girls (mean age: 9.6 years) 5–20 years of age, were compared with a control group, 14 boys (mean age: 8.84 years) and 6 girls (mean age: 9.2 years), 5–20 years of age. With the autism subjects, in writing, 56.8% were left-handers, 10.8% were right-handers and 32.4% were ambiguous. In throwing, 48.65% were left-handers, 16.22% were right-handers, and 35.13% were ambiguous. Ten percent of controls were left-handers by writing and throwing and 90% were right-handers. For patients, 83.7% had left-eye preference and 16.3% had the right-eye preference, and 70% of the controls were right-eye dominant, and 30% were left-eye dominant. Nasal dominance was assessed 24 times between 8 am and 8 pm at 30-minute intervals. Summarizing nasal cycle measures they state:

> Seven children with autism had the left nasal dominance for all measurements. Two patients for only one time in 24 measurements and 2 patients only 2 times had the right nasal dominance. Four patients had the right nasal dominance for 12 or more times in 24 measurements. In summary, a majority of patients with autism had the left nasal dominance for major portion of the day-time. However, in controls the rates of right and left nasal dominance were about equal. The mean use number of left nostril in 24 assessments in autistic children (19.59±4.32) was more than controls (11.75±1.97) (t=7.67, P=.00).[106]

They conclude "Autism and early language impairment may be associated with left handedness, eyedness and nasal dominance.... These results show that the patients with autism had no normal nasal cycle; probably they had almost continuous left."

In sum, one might conclude that selective unilateral autonomic activation is a simple but useful mechanism that exploits the unique independent and lateral nature of the autonomic innervation to the organs, tissues, and brain. Henry[36] further comments:

"Anatomical pathways provide the left cervical vagus afferent and efferent fibers with access to parasympathetic control of the heart and multiple other visceral organs; pharyngeal muscles of vocalization; a limited somatosensory representation of the head and neck; and a widespread array of autonomic, reticular, and limbic structures of the brainstem and both hemispheres. Therapeutic VNS appears to have remarkably little affect on the vagal parasympathetic visceroeffectors. The common reversible adverse effects of VNS mainly involve vocalization and somatic sensation. Experimental and human studies most strongly support altered activities of the reticular activating system, the central autonomic network, the limbic system, and the diffuse noradrenergic projection system as modalities of seizure antagonism."

However, it may also be important to explore potential VNS effects on the endogenous ultradian rhythms. It is likely that such effects exist and that they may play a central role in the regulation of a range of disorders where imbalances occur. The ANS-CNS rhythm manifests like an internal pendulum of lateral activities, and it may be a shift in this rhythm that plays a useful therapeutic role.[14,15] It is known that UFNB can indeed affect the balance of various ANS-CNS functions and yogis had viewed this pendulum as a balance of "yin and yang" activities that are central to health that can now be viewed with an extended BRAC concept.[15,16,43]

References

1. Saper CB, Loewy AD, Swanson LW, et al. Direct hypothalamo-autonomic connections. *Brain Res*. 1976;117:305-312.
2. Saper CB. Organization of cerebral cortical afferent systems in the rat. II. Hypothalamocortical projections. *J Comp Neurol*. 1985;237:21-46.
3. Saper CB. Hypothalamic connections with the cerebral cortex. *Prog Brain Res*. 2000;126:39-48.
4. Karplus J, Kreidl A. Gehirn und sympathicus. I. Zwischenhirnbasis und halssympatheticus [German]. *Pfluger Arch Gesamte Physiol*. 1909;129:138-144.
5. Karplus J, Kreidl A. Gehirn und Sympathicus. II. Ein sympathicuszentrum im zwischenhirn [German]. *Pfluger Arch Gesamte Physiol*. 1910;135:401-416.
6. Karplus J, Kreidl A. Gehirn und sympathicus. III. Sympathicusleitung im gehirn und halsmark [German]. *Pfluger Arch Gesamte Physiol*. 1912;143:107-127.
7. Karplus J, Kreidl A. Uber Totallexstirpationen einer und beider Grosshirnhemispharen an Affen (Macacus rhesus) [German]. *Arch Anat Phsyiol (Physiol Abt)*. 1914:155-212.
8. Swanson LW. The hypothalamus. In: A. Bjorkland, T. Hokfelt, Swanson L, eds. *Handbook of Chemical Neuroanatomy, Vol. 5, Integrated Systems of the CNS*. Amsterdam, The Netherlands: Elsevier Science Publishers BV; 1987:1-124.
9. Beattie J. Hypothalamic mechanisms. *Can Med Assoc J*. 1932;26:400-405.
10. Beattie J, Sheehan D. The effects of hypothalamic stimulation on gastric motility. *J Physiol*. 1934;81:218-227.
11. Beattie J, Kerr A. The effects of diencephalic stimulation on urinary bladder tonus. *Brain*. 1936;59:302-314.
12. Ranson S, Magoun H. The hypothalamus. *Ergeb Physiol*. 1939;41:56-163.
13. Hess WR. *Diencephalon, Autonomic and Extrapyridimal Functions*. New York, NY: Grune and Stratton; 1954.
14. Shannahoff-Khalsa D. Lateralized rhythms of the central and autonomic nervous systems. *Int J Psychophysiol*. 1991;11:225-251.

15. Shannahoff-Khalsa DS. *Stress Technology Medicine, A New Paradigm for Stress and Considerations for Self-regulation*. New York, NY: Marcel Dekker Inc.; 1991.
16. Shannahoff-Khalsa DS. *Psychophysiological States: The Ultradian Dynamics of Mind-Body Interactions*. In: Bradley RJ, Harris RA, Jenner P, eds. *International Review of Neurobiology*. vol 80. San Diego, Calif: Academic Press/Elsevier Scientific Publications; In press.
17. Kayser R. Die exacta messung der luftdurchgangigkeit der nase [German]. *Archives of Laryngology and Rhinology*. 1895;3:101-120.
18. Beickert P. Halbseitenrhythmus der vegetativen innervation [German]. *Arch Ohr Nos Kehl Hdk*. 1951;157:404-411.
19. Werntz DA, Bickford RG, Bloom FE, Shannahoff-Khalsa DS. Alternating cerebral hemispheric activity and the lateralization of autonomic nervous function. *Hum Neurobiol*. 1983;2:39-43.
20. Shannahoff-Khalsa D. The ultradian rhythm of alternating cerebral hemispheric activity. *Int J Neurosci*. 1993;70:285-298.
21. Kayser R. Uber den Weg der Athmungsluft durch die Nase [German]. *Z Ohrerlheilh*. 1889;20:96-106.
22. Eccles R. Nasal airflow in health and disease. *Acta Otolaryngol*. 2000;120:580-595.
23. Hasegawa M, Kern EB. Variations resistance in man: a rhinomanometric study of cycle in 5O human subjects. *Rhinology*. 1978;16:20-29.
24. Heetderks DR. Observations on the reaction of the nasal mucous membranes. *Am J Med Sci*. 1927;174:231-244.
25. Stoksted P. Rhinometric measurements for determination of the nasal cycle. *Acta Otolaryngol Suppl*. 1953;109:159-175.
26. Shannahoff-Khalsa DS, Kennedy B, Yates FE, et al. Ultradian rhythms of autonomic, cardiovascular, and neuroendocrine systems are related in humans. *Am J Physiol*. 1996;270:R873-R887.
27. Shannahoff-Khalsa DS, Kennedy B, Yates FE, et al. Low-frequency ultradian insulin rhythms are coupled to cardiovascular, autonomic, and neuroendocrine rhythms. *Am J Physiol*. 1997;272:R962-R968.
28. Shannahoff-Khalsa DS, Yates FE. Ultradian sleep rhythms of lateral EEG, autonomic, and cardiovascular activity are coupled in humans. *Int J Neurosci*. 2000;101:21-43.
29. Shannahoff-Khalsa DS, Gillin JC, Yates FE, et al. Ultradian rhythms of alternating cerebral hemispheric EEG dominance are coupled to rapid eye movement and non-rapid eye movement stage 4 sleep in humans. *Sleep Med*. 2001;2:333-346.
30. Kennedy B, Ziegler MG, Shannahoff-Khalsa DS. Alternating lateralization of plasma catecholamines and nasal patency in humans. *Life Sci*. 1986;38:1203-1214.
31. Kleitman N. *The Nature of Dreaming*. London, England: Churchill Press; 1961.
32. Kleitman N. *Phylogenetic, Ontogenetic and Environmental Determinants in the Evolution of Sleep-Wakefulness Cycles*. Baltimore, Md: The Williams and Wilkins Co.; 1967.
33. Kleitman N. Basic rest-activity cycle–22 years later. *Sleep*. 1982;5:311-317.
34. Lavie P, Kripke DF. Ultradian circa 11/2 hour rhythms: a multioscillatory system. *Life Sci*. 1981;29:2445-2450.
35. Foley J, DuBois F. Quantitative studies of the vagus nerve in the cat. I. The ration of sensory and motor studies. *J Comp Neurol*. 1937;67:49-67.
36. Henry TR. Therapeutic mechanisms of vagus nerve stimulation. *Neurology*. 2002;59(suppl 4):S3-S14.
37. Levy M, Martin P. *Neural Control of the Heart*. Bethesda, Md: American Physiological Society; 1979.
38. Levy MN, Ng ML, Zieske H. Functional distribution of the peripheral cardiac sympathetic pathways. *Circ Res*. 1966;19:650-661.
39. Furnival CM, Linden RJ, Snow HM. Chronotropic and inotropic effects on the dog heart of stimulating the efferent cardiac sympathetic nerves. *J Physiol*. 1973;230:137-153.

40. Hondeghem LM, Mouton E, Stassen T, et al. Additive effects of acetylcholine released by vagal nerve stimulation on atrial rate. *J Appl Physiol*. 1975;38:108-113.
41. Hamlin RL, Smith CR. Effects of vagal stimulation on S-A and A-V nodes. *Am J Physiol*. 1968;215:560-568.
42. Shannahoff-Khalsa D. Unilateral forced nostril breathing: basic science, clinical trials, and selected advanced techniques. *Subtle Energies Energy Med J*. 2001;12:79-106.
43. Shannahoff-Khalsa D. *Kundalini Yoga Meditation: Techniques Specific for Psychiatric Disorders, Couples Therapy, and Personal Growth*. New York, NY: W. W. Norton & Company; 2006.
44. Werntz DA, Bickford RG, Bloom FE, et al. Cerebral Hemispheric Activity and Autonomic Nervous Function. Paper presented at: 10th Annual Meeting of the Society for Neuroscience. November 9-14, 1980; Cincinnati, Oh.
45. Werntz DA, Bickford RG, Bloom FE, et al. Selective cortical activation by altering autonomic function. Abstract presented at: Annual Meeting of the Western EEG Society Meeting. February 21, 1981; Reno, Nev.
46. Werntz DA, Bickford RG, Shannahoff-Khalsa D. Selective hemispheric stimulation by unilateral forced nostril breathing. *Hum Neurobiol*. 1987;6:165-171.
47. Servit Z, Kristof M, Strejckova A. Activating effect of nasal and oral hyperventilation on epileptic electrographic phenomena: reflex mechanisms of nasal origin. *Epilepsia*. 1981;22:321-329.
48. Klein R, Pilon D, Prosser S, et al. Nasal airflow asymmetries and human performance. *Biol Psychol*. 1986;23:127-137.
49. Shannahoff-Khalsa DS, Boyle MR, Buebel ME. The effects of unilateral forced nostril breathing on cognition. *Int J Neurosci*. 1991;57:239-249.
50. Jella SA, Shannahoff-Khalsa DS. The effects of unilateral forced nostril breathing on cognitive performance. *Int J Neurosci*. 1993;73:61-68.
51. Telles S, Raghuraj P, Maharana S, et al. Immediate effect of three yoga breathing techniques on performance on a letter-cancellation task. *Percept Mot Skills*. 2007;104:1289-1296.
52. Baglio S, Bucolo M, Fortuna L, et al. MEG signals spatial power distribution and gamma band activity in yoga breathing exercises. Paper presented at: Conference Proceedings of the IEEE Engineering in Medicine and Biology Society. October 23-26, 2002; Houston, Tex.
53. Block RA, Arnott DP, Quigley B, et al. Unilateral nostril breathing influences lateralized cognitive performance. *Brain Cogn*. 1989;9:181-190.
54. Sanders B, Lattimore C, Smith K, et al. Forced single-nostril breathing and cognition. *Percept Mot Skills*. 1994;79:1499-1506.
55. Schiff BB, Rump SA. Asymmetrical hemispheric activation and emotion: the effects of unilateral forced nostril breathing. *Brain Cogn*. 1995;29:217-231.
56. Shannahoff-Khalsa DS, Beckett LR. Clinical case report: efficacy of yogic techniques in the treatment of obsessive compulsive disorders. *Int J Neurosci*. 1996;85:1-17.
57. Shannahoff-Khalsa D, Ray L, Levine S, et al. Randomized controlled trial of yogic meditation techniques for patients with obsessive compulsive disorders. *CNS Spectr*. 1999;4:34-46.
58. Sercer A. Research on the homolateral reflex of the nasal cavity on the lung. *Acta Otolaryng*. 1930;14:82-90.
59. Samzelius-Lejdstrom I. Researches with the bilateral troncopneumograph on the movements of the respiratory mechanisms during breathing. *Acta Otolaryng*. 1939;35(suppl):3-104.

60. Stoksted P. Obstructions in the nose and their influence on the pulmonary functions. *Acta Otorhinolar*. 1960;158(suppl):110.
61. Drettner B. Pathophysiological relationship between the upper and lower airways. *Ann Otol Rhinol Laryngol*. 1970;79:499-505.
62. Wotzilka G, Schramek J. Tierexperimentelle Untersuchungen uber den Weg des Inspirationsstromes jeder Nasenseite in die Lunge [German]. *Mschr Ohrenheilk*. 1930;64:580-585.
63. Backon J. Changes in blood glucose levels induced by differential forced unilateral nostril breathing, a technique which affects both brain hemisphericity and autonomic activity. *Med Science Res*. 1988;16:1197-1199.
64. Backon J, Kullok S. Effect of forced unilateral nostril breathing on blink rates: relevance to hemispheric lateralization of dopamine. *Int J Neurosci*. 1989;46:53-59.
65. Backon J, Matamoros N, Ticho U. Changes in intraocular pressure induced by differential forced unilateral nostril breathing, a technique that affects both brain hemisphericity and autonomic activity. A pilot study. *Graefes Arch Clin Exp Ophthalmol*. 1989;227:575-577.
66. Mohan SM, Reddy SC, Wei LY. Modulation of intraocular pressure by unilateral and forced unilateral nostril breathing in young healthy human subjects. *Int Ophthalmol*. 2001;24:305-311.
67. Chen JC, Brown B, Schmid KL. Effect of unilateral forced nostril breathing on tonic accommodation and intraocular pressure. *Clin Auton Res*. 2004;14:396-400.
68. Benton LA, Yates FE. Ultradian adrenocortical and circulatory oscillations in conscious dogs. *Am J Physiol*. 1990;258:R578-R590.
69. Orr WC, Hoffman HJ. A 90-min cardiac biorhythm: methodology and data analysis using modified periodograms and complex demodulation. *IEEE Trans Biomed Eng*. 1974;21:130-143.
70. Shannahoff-Khalsa DS, Kennedy B. The effects of unilateral forced nostril breathing on the heart. *Int J Neurosci*. 1993;73:47-60.
71. Mohan S, Wei L. Modulation of pulse rate by unilateral nostril breathing. *J Indian Psychol*. 2002;20:32-37.
72. Dane S, Caliskan E, Karasen M, et al. Effects of unilateral nostril breathing on blood pressure and heart rate in right-handed healthy subjects. *Int J Neurosci*. 2002;112:97-102.
73. Telles S, Nagarathna R, Nagendra HR. Breathing through a particular nostril can alter metabolism and autonomic activities. *Indian J Physiol Pharmacol*. 1994;38:133-137.
74. Telles S, Nagarathna R, Nagendra HR. Physiological measures of right nostril breathing. *J Altern Complement Med*. 1996;2:479-484.
75. Friedell A. Automatic attentive breathing in angina pectoris. *Minn Med*. 1948;31:875-881.
76. Konno A. Air flow and resistance in the nasal cavity. 2. Bilateral rhinometry using a pneumotachometer. Its principles and clinical application [Japanese]. *Nippon Jibiinkoka Gakkai Kaiho*. 1969;72:49-65.
77. Takagi K, Kobayasi S. Skin pressure-vegetative reflex. *Acta Med et Biol*. 1955;4:31-57.
78. Takagi K, Sakurai T. A sweat reflex due to pressure on the body surface [Japanese]. *Jap J Physiol*. 1950;1:22-28.
79. Rao S, Potdar A. Nasal airflow with body in various positions. *J Appl Physiol*. 1970;28:162-165.
80. Haight JJ, Cole P. Reciprocating nasal airflow resistances. *Acta Otolaryngol*. 1984;97:93-98.
81. Haight JS, Cole P. Unilateral nasal resistance and asymmetrical body pressure. *J Otolaryngol Suppl*. 1986;16:1-31.
82. Cole P, Haight J. Posture and the nasal cycle. *Am Otol Rhinol Laryngol*. 1986;95:233-237.
83. Cole P, Haight JS. Posture and nasal patency. *Am Rev Respir Dis*. 1984;129:351-354.
84. Morris GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. *Neurology*. 1999;53:1731-1735.

85. Ben-Menachem E, Hamberger A, Hedner T, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. *Epilepsy Res*. 1995;20:221-227.
86. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology*. 1998;51:48-55.
87. Hatton KW, McLarney JT, Pittman T, et al. Vagal nerve stimulation: overview and implications for anesthesiologists. *Anesth Analg*. 2006;103:1241-1249.
88. Salinsky MC, Uthman BM, Ristanovic RK, et al. Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open-extension trial. Vagus Nerve Stimulation Study Group. *Arch Neurol*. 1996;53:1176-1180.
89. DeGiorgio CM, Schachter SC, Handforth A, et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia*. 2000;41:1195-1200.
90. *Physician's Manual*. VNS TherapyTM Pulse Model 102 Generator and VNS TherapyTM Pulse Duo Model 102R Generator. Houston, Tex: Cyberonics Inc; 2004.
91. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry*. 2000;47:276-286.
92. Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology*. 2001;25:713-728.
93. Rush AJ, Sackeim HA, Marangell LB, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry*. 2005;58:355-363.
94. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry*. 2005;58:347-354.
95. Nahas Z, Marangell LB, Husain MM, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J Clin Psychiatry*. 2005;66:1097-1104.
96. Sackeim HA, Rush AJ, Marangell LB, et al. Long-term antidepressant effects of vagus nerve stimulation (VNS) in treatment-resistant depression. Paper presented at: Annual Meeting of the American College of Neuropsychopharmacology. December 12–16, 2004; San Juan, PR.
97. Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol Psychiatry*. 2002;51:280-287.
98. George MS, Rush AJ, Sackeim HA, et al. Vagus nerve stimulation (VNS): utility in neuropsychiatric disorders. *Int J Neuropsychopharmacol*. 2003;6:73-83.
99. Husted D, Shapira N. A review of the treatment for refractory obsessive-compulsive disorder: from medicine to deep brain stimulation. *CNS Spectr*. 2004;9:833-847.
100. Pallanti S, Hollander E, Goodman WK. A qualitative analysis of nonresponse: management of treatment-refractory obsessive-compulsive disorder. *J Clin Psychiatry*. 2004;65(suppl 14):6-10.
101. Nemeroff CB, Mayberg HS, Krahl SE, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. *Neuropsychopharmacology*. 2006;31:1345-1355.
102. Group VNSS. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures.

Neurology. 1999;45:224-230.
103. George MS, Sackeim HA, Marangell LB, et al. Vagus nerve stimulation. A potential therapy for resistant depression? *Psychiatr Clin North Am*. 2000;23:757-783.
104. Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. *Neurosci Biobehav Rev*. 2005;29:493-500.
105. Rosenbaum JF, Heninger G. Vagus nerve stimulation for treatment-resistant depression. *Biol Psychiatry*. 2000;47:273-275.
106. Dane S, Balci N. Handedness, eyedness and nasal cycle in children with autism. *Int J Dev Neurosci*. 2007;25:223-226.