HANDBUCH DER VAGUS STIMULATION

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Index

A. The vagus (vagus nerve)

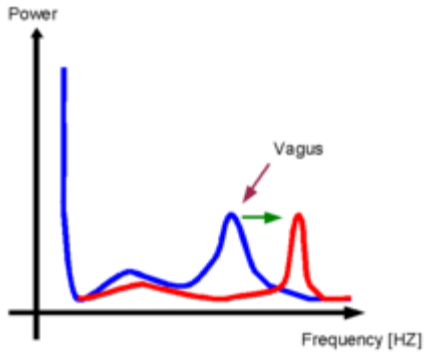
The vagus nerve, simply referred to as the vagus, is a central cerebral nerve. It originates from the medulla oblongata, the transition from the spinal column to the brain. It is the largest nerve of the parasympathetic nervous system and is involved in the regulation of activity of almost all internal organs. It is the second-largest nerve in the body after the spinal nerve system. The activity of the vagus controls the heartbeat as well as protein production, among other things.

The vagus has sensory as well as motor performance functions. It uses these to regulate the brain in terms of organ and process activities that are not carried out voluntarily, in other words consciously. The name comes from the Latin “vagus”, meaning “wanderer”. The nerve therefore moves through large parts of the head, ear and neck region and the upper body, focusing on heart and digestive system activity. It is the strongest parasympathetic nerve of the vegetative nervous system, and because of this, it has a crucial role in many body processes. Its often-coined description as a recovery nerve stems from its importance in allowing the whole body to relax. This process also highlights its significance in a multitude of diseases and clinical pictures.[1] 80% of the nerve serves to transmit information from the body to the brain, while 20% is used to transfer information from the brain to the organs. The backflow of information can then directly influence the brain itself. Bacteria of the intestinal flora may be back-stimulated through a chemical reaction of the vagus.

The activity of the vagus may be observed via a so-called heart rate variability analysis, or HRV.[2] This is derived directly from the measurement of electrical heart activity and shown in the ECG. The following frequency band images are observed in an analysis of the heart rates.

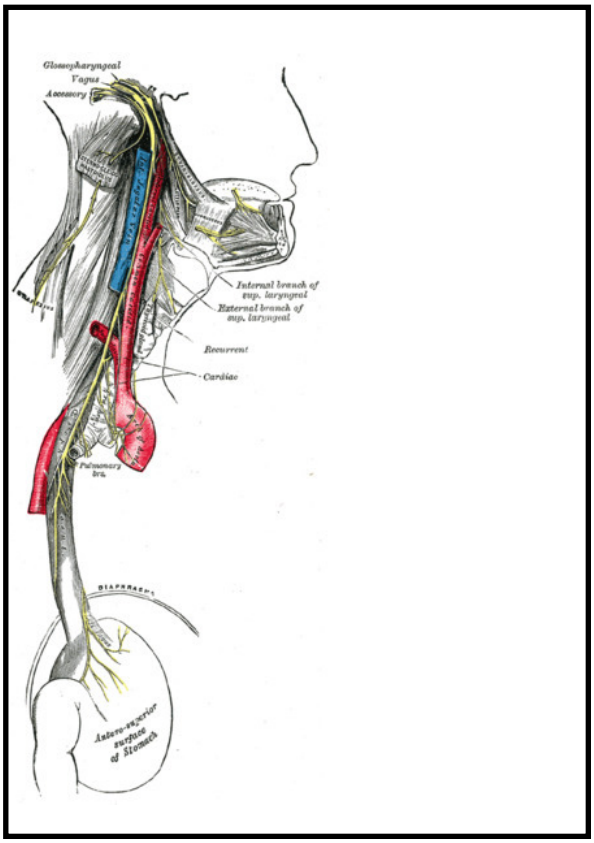
[1] Thomas Ropp, 5 September 2017.

[2] Clancy/Mary/Witte/Greenwood/Deuchars/ Deuchars, Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity, School of Medicine and School of Biomedical Sciences, University of Leeds, Leeds, UK, LS2 9JT.



Shift in the heart rate spectrum on exertion (red) vs at rest (blue)

The activity of the vagus is directly based on the heart activity rhythm. As the heart rate increases, the vagus activity then reaches a higher frequency. In return, the activity of the vagus can reduce the heart rate and cause a decrease in blood pressure.



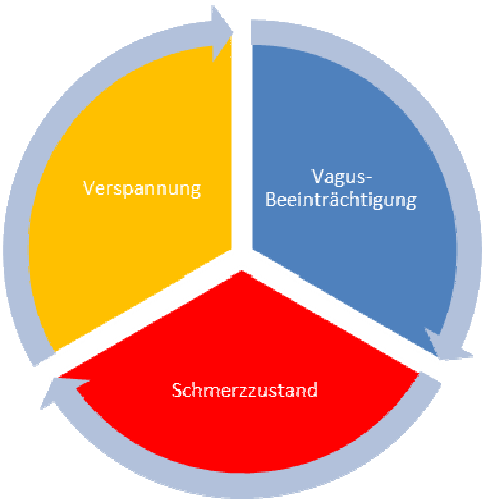
B. The vagus in the context of the development of diseases

Damage to the vagus may be the result of diabetes, mercury, botox, alcoholism, viral infections of the upper respiratory tract or ear, inflammations, stress or anxiety disorders, but also poor physical posture. In turn, this damage may trigger symptoms itself as the body's ability to relax is restricted.[3] The vagus has a crucial role in controlling heart rate variability (HRV). The higher the heart rate bandwidth, the healthier the person is often classified as. The HRV reflects the body's ability to adjust to various challenges, stress, activity and rest and adapt bodily functions accordingly. If the body can no longer adjust, it falls into a constant state of overtension or undertension.[4] This is also observed in patients with high blood pressure. These patients typically cannot achieve a corresponding reduction of their blood pressure via the HRV due to increased sympathetic nerve activity.[5]

If any pain is present, damages to the vagus may even lead to a cycle of pain. The general entry point is poor muscle function due to incorrect loading or underloading, resulting in poor posture that eventually triggers a

[3] Rosenberg, p. 3.
[4] Rosenberg, p. 69 ff.
[5] Sartori/Stein/Coronel/Edler/Della Méa Plentz, Effects of Transcutaneous Electrical Nerve Stimulation in Autonomic Nervous System of Hypertensive Patients: A Randomized Controlled Trial, Current Hypertension Reviews, 2018, 14, 66-71.

reduction in vagus activity again. This is followed by a lack of body relaxation, with increasing muscle tension and reamplified pain and a further reduction in physical activity, and so the cycle of pain continues and grows in severity.



It is understood that the activity of the vagus and its impact on heart rate variability also affects the efficiency of the immune system.[6] If the vagus is out of step, this also seems to affect the immune system and the ability of the body to provide a corresponding adequate immune response in many cases. This may be fatal for both types of "extreme" patients, as underactivity weakens the immune defence system and hyperactivity enables the body to attack itself, as is the case in rheumatoid arthritis, for example.[7] Related experiments on animals verified on a physiological level that stimulation of the vagus nerve triggers a corresponding positive immune reaction, while a blockade achieves the opposite effect.[8]

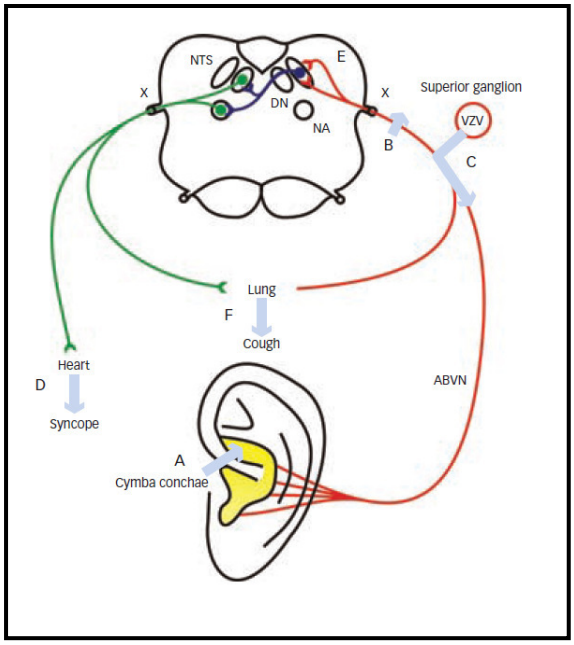


Illustration from: Ellrich, Transcutaneous Vagus Nerve Stimulation, European Neurological Review, 2011;6(4): 254-6.

Lung/Heart connection: D

Cough: F

Cymba conchae: A

Superior ganglion: ABVN VZV

Varicella zoster virus: VZV

Vagus nerve: X

C. Vagus nerve stimulation (VNS)

Vagus nerve stimulation (VNS) uses fine electrical currents to activate the vagus nerve.

[6] Clancy/Mary/Witte/Greenwood/Deuchars/ Deuchars, Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity, School of Medicine and School of Biomedical Sciences, University of Leeds, Leeds, UK, LS2 9JT; Douglas Fox, Can Zapping the Vagus Nerve Jump Start Immunity?, Nature, 04/05/2017.

[7] Douglas Fox, Can Zapping the Vagus Nerve Jump Start Immunity?, Nature, 04/05/2017.

[8] Douglas Fox, Can Zapping the Vagus Nerve Jump Start Immunity?, Nature, 04/05/2017.

Because the vagus has hardly any pain-conducting fibres, this can be tolerated well. Two different types are possible: stimulator implantation, or stimulation via extracorporeal electrodes (transcutaneous stimulation). This stimulates both type A and type B fibres. The following are reached: the solitary nucleus (SN), the amygdala, the dorsal raphe nuclei, the locus coeruleus, the nucleus ambiguus, the motor dorsal nucleus of the vagus nerve, the parabrachial nucleus, the hypothalamus and the thalamus.

The goal of vagus stimulation is to achieve normalisation of the activity of the vagus. It may be used both for hyperactivity of the vagus and for chronic underactivity. The restoration of the normal functioning of the vagus nerve should then be accompanied by the ability of the body to adjust the heart rate variability (HRV). If the body is able to variably adjust the HRV according to everyday requirements and the physical reactions to diseases needed, the body's out-of-step self-healing ability typically normalises.[9]

Numerous studies on humans and animals describe various aspects of VNS mechanisms. The solitary nucleus is the central receiver of vagal afferents and is modulated by VNS in animal models in terms of function and depending on the stimulation. The solitary nucleus transmits directly to the raphe nuclei in the brain stem, the main source of serotonin in the brain, and to the locus coeruleus, the main source of noradrenaline in the brain. This also explains the altered neurotransmitter levels in patients following VNS which could result in an antispasmodic effect. In patients with refractory epilepsy, a significant increase in bilateral thalamic circulation, which could clarify the known increased vigilance of VNS patients, alongside an improvement in the interictal EEG (fewer spikes and larger spike-free periods) is observed through VNS.[10]

If the vagus is in a normal condition, it is able to support the body in suppressing inflammatory molecules such as tumour necrosis factor alpha (TNF-alpha) or interleukin 6 and in activating T-cells of the immune defence system.[11] Furthermore, an improvement in cerebral circulation and protection of the brain tissue affected by strokes have been observed after using stimulation.[12] This effect may lead to

[9] Rosenberg, p. 69 ff.

[10] Furmaga: Comparison of ΔFosB immunoreactivity induced by vagal nerve stimulation with that caused by pharmacologically diverse antidepressants. Ed.: J Pharmacol Exp Ther. 2012, doi:10.1124/jpet.111.188953.; Ben-Menachem et al.: Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. Ed.: Epilepsy Research. 1995; Henry et al.: Significant bilateral changes in blood flow have been observed during VNS Therapy. Ed.: Epilepsia. 1998; Koo et al.: VNS Therapy induces progressive EEG changes. Ed.: J Clin Neurophysiol. 2001.

[11] Douglas Fox, Can Zapping the Vagus Nerve Jump Start Immunity?, Nature, 04/05/2017.

[12] Ilknur Ay, Vitaly Napadow a,b , Hakan Ay, Electrical Stimulation of the Vagus Nerve

improved results and healing processes in the rehabilitation of stroke patients.[13]

I. Vagus stimulation with implants

The first VNS implants started to be used as early as 1988. In 1997, the company Cyberbionics approved an implantable stimulator in the USA indicated for epilepsy treatment. Studies on depression and headache were initiated based on this approval, which were approved in 2005. Over the years, these implants have been used in over 25,000 patients. Implants are similar to pacemakers in terms of shape. Surgery to insert the implant is also similar to pacemaker surgery. It is understood that VNS causes a modulation of the nerve pathways and related brain activity.

In VNS, a procedure is carried out whereby a stimulation device similar to a pacemaker is implanted in the chest region underneath the skin, which is typically connected to the left vagus nerve via an electrode. The implantable generator sends regular electrical pulses (usually every 5 minutes for 30 seconds) via the vagus nerve to the brain, thereby resulting in an antispasmodic and anti-depressive effect. The efficacy and safety of VNS have been confirmed in a range of studies over 20 years. These demonstrated that VNS achieves a reduction in seizures of 50% or more in 55% of patients with drug-resistant epilepsy.[14] Long-term studies have clarified that even greater reductions in seizures of up to 76% can be expected in patients treated with VNS for more than 2 years.[15] Alongside a decrease in the frequency of seizures, VNS can reduce the duration and severity of seizures, the duration of the postictal phase and the prevalence of seizures.[16] A Cochrane review of 4 randomised double-blind studies on VNS came to the conclusion that high doses of VNS cause a greater reduction in seizures than low

Dermatome in the External Ear is Protective in Rat Cerebral Ischemia, Brain Stimulation 8 (2015) 7-12; Ilknur Ay, Rena Nasser, Bruce Simon, Hakan Ay, Transcutaneous Cervical Vagus Nerve Stimulation Ameliorates Acute Ischemic Injury in Rats, Brain Stimulation 9 (2016) 166-173.

[13] Dawson/Pierce/Dixit/Kimberley/Robertson/ Tarver/Hilmi/McLean/Forbes/Kilgard/Rennaker/ Cramer/Walters/Navzer, Safety, Feasibility, and Efficacy of Vagus Nerve Stimulation Paired with Upper-Limb Rehabilitation After Ischemic Stroke, Stroke, Jan. 2016.

[14] Morris et al.: Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Ed.: Neurology. 2013, doi:10.1212/WNL.0b013e3182a393d1.

[15] Elliott et al.: Efficacy of vagus nerve stimulation over time: review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS > 10 years. Ed.: Epilepsy Behaviour. 2011, doi:10.1016/j.yebeh.2010.12.042.

[16] Orosz et al.: Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. 2014, doi:10.1111/epi.12762; Helmers: Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy. Ed.: Epilepsy Behav. 2011, doi:10.1016/j.yebeh.2011.07.020; Panebianco et al.: Vagus nerve stimulation for partial seizures. Ed.: Cochrane Database Syst Rev. 2015, doi:10.1002/14651858.

doses of VNS. The most common side effects of VNS are cough, hoarseness and dysphonia. However, these side effects typically only occur while the device is stimulating and recede over time. For refractory depression the long-term response rate is around 50%, and around 20% of patients achieve complete remission after 2 years. The German Society for Epileptology recommends VNS implants for difficult-to-treat epilepsies if 2 antiepileptics (or combinations of antiepileptics) have not achieved freedom from seizures and the patient is not a candidate for epilepsy surgery or has refused this.[17]

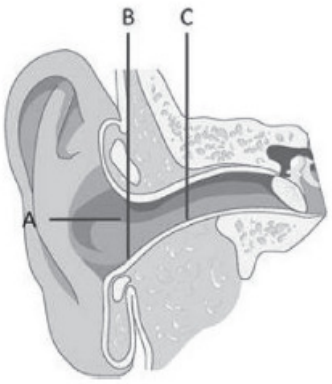
During the operation itself, the vagus nerve situated near the left main artery is located via a skin incision in the neck. Two electrodes are wrapped around this, which are connected to a cable. This cable runs down through the collarbone and is connected to a stimulation device underneath which is implanted between the subcutaneous fatty tissue and the pectoral muscle.

[17] Morris et al.: Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. In: Neurology (ed.): Nov. 10; 53(8): 1731-1735. 1999; Berry et al.: A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. Ed.: Med Devices. Auckland 2013, doi:10.2147/MDER.S41017; Fröscher, Theodor W May: Schwer behandelbare Epilepsie [Difficult-to-treat Epilepsy] 079. Ed.: German Society for Epileptology. June 2016 (izepilepsie.de).

II. Transcutaneous vagus nerve stimulation (t-VNS)

The great results of vagus stimulation through implants are counteracted by the high risks and irreversibility of surgery and the huge costs involved. For these reasons, the development of external vagus stimulation without implants has been promoted. This stimulation uses external electrodes and an external stimulator. The stimulation pulses are equivalent to the pulses of implanted stimulators.

Transcutaneous vagus nerve stimulation (tVNS) is based on the knowledge that a vagus nerve branch – the auricular branch of the vagus nerve (ABVN) – serves the skin of the ear muscle in the region of the concha.

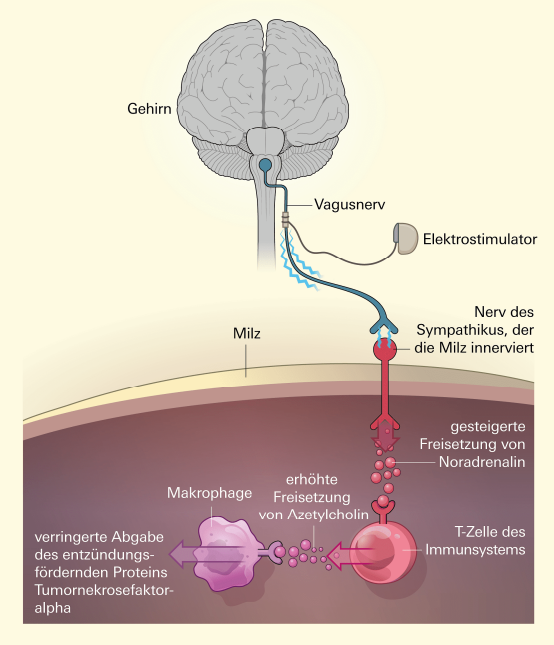


cavum conchae (A) and external (B) and internal (C)
[18]

[18] Illustration from: Bermejo/López/Larraya/ Chamorro/Cobo/Ordóñez/Vega, Innervation of the Human Cavum Conchae and Auditory Canal: Anatomical Basis for Transcutaneous Auricular Nerve Stimulation, BioMed Research International Volume 2017.

This nerve arm may be stimulated transcutaneously, i.e. through the skin, using electrical pulses. Surgical intervention is not necessary as a result. In the first randomised double-blind study with tVNS, neither a dose-effect relation nor any difference in the response rates could be demonstrated between implants and external stimulation. The reduction in seizures with tVNS in this study in the active group was 23.4%. It is believed that the stimulation of the auricular branch of the vagus nerve excites the vagus nerve. As in conventional VNS, this excitement then travels along the brain stem to the high-altitude centres of the brain, thereby achieving an antispasmodic effect. Using a special ear electrode, the pulses are transmitted through the skin to the branch of the vagus nerve.

Transcutaneous vagus nerve stimulation (tVNS) may trigger parasympathetic activities by activating the autonomous brain stem nuclei, whereby tVNS modulates the immune system function by activating the cholinergic anti-inflammatory pathway. tVNS is therefore beneficial for modulating inflammatory reactions. The concentrations of proinflammatory cytokine in serum and NF-kappa B p65 (NF-κB p65) in tissue have already been demonstrated in anaesthetised rats affected by endotoxaemia. tVNS therefore suppresses proinflammatory cytokine levels in serum, such as tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6), as well as NF-kappa B p65 expressions in lung tissue. Stimulation also reduces LPS-induced high TNF-α levels and NF-κB signals. In this case, tVNS may be used to suppress inflammatory reactions via α nAChR-mediated cholinergic anti-inflammatory pathways.[19]

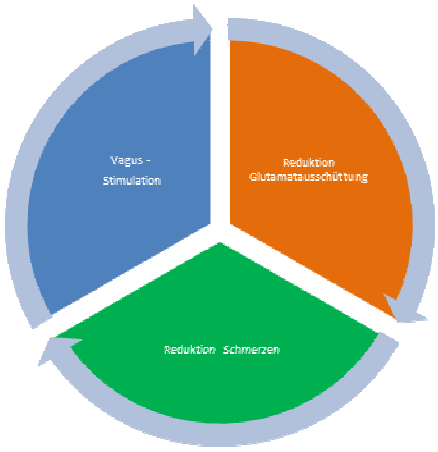


Studies have shown that transcutaneous vagus nerve stimulation (tVNS) significantly

[19] Zhao/He/Hong Jing/Liu/Rong/Ben/Liu/Zhu, Transcutaneous Auricular Vagus Nerve Stimulation Protects Endotoxemic Rat from Lipopolysaccharide-Induced Inflammation, Evidence-Based Complementary and Alternative Medicine Volume 2012.

improves the HRV. This is attributable to an increase in parasympathetic activity. The sympathetic activity of the muscles is lowered, which is associated with significant health benefits.[20]

The stimulation causes a reduction in glutamate release during feedback to the brain. The extent of this release is directly connected to the development of a range of pain conditions. The reduction in the release may therefore trigger a reduction in pain.



D. Area of application of vagus stimulation

Because vagus stimulation may have an effect on the normalisation of the immune system response, as well as heart rate variability, it is of no surprise that vagus stimulation has demonstrated good results in the treatment of a range of diseases and clinical pictures.

Low-frequency pulses should be used to reduce blood pressure and for a resulting, generally relaxing effect, while high-frequency pulses are instead intended to cause a stimulation in blood pressure.[21]

I. Pain and migraine

A major focus of vagal stimulation is on pain conditions, likely also considering its role in supporting the body's ability to relax and the reduced glutamate release in the intestine (see above). To this extent, results have been demonstrated in the following areas: back pain, [22] and pain in the region of the shoulder, neck and head.[23] For headaches, results have even been shown to be significantly superior compared to traditional treatment results.[24]

For migraine[25] a significant reduction in headache attacks of more than 50% may be

[20] Clancy/Mary/Witte/Greenwood/Deuchars/ Deuchars, Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity, School of Medicine and School of Biomedical Sciences, University of Leeds, Leeds, UK, LS2 9JT.

[21] Sartori/Stein/Coronel/Edler/Della Méa Plentz, Effects of Transcutaneous Electrical Nerve Stimulation in Autonomic Nervous System of Hypertensive Patients: A Randomized Controlled Trial, Current Hypertension Reviews, 2018, 14, 66-71.

[22] Rosenberg, p. 115.

[23] Rosenberg, Accessing the healing power of the vagus nerve, Berkley 2017, p. 102

[24] Morris et al., Cost-effectiveness analysis of non-invasive vagus nerve stimulation for the treatment of chronic cluster headache, The Journal of Headache and Pain (2016) 17:43.

[25] Goadsby/Grosberg/Mauskop/Cady/Simmons, Effect of noninvasive vagus nerve stimulation on acute migraine: An open-label pilot study, Cephalalgia 2014, Vol. 34(12) 986-993.

expected, [26] which is even comparable with the medications naratriptan, naproxen and dicoflenac[27], but no side effects related to the intake of medications are demonstrated. In the treatment of cluster headache attacks,[28] good results have been achieved here as well through preventive stimulation of the vagus nerve[29] (i.e. stimulation performed daily) which led to a significant reduction in the overall number of attacks.

Overall, a general reduction in pain was observed under vagus nerve stimulation. Studies have also been able to demonstrate that patients undergoing tVNS experienced a general decrease in the pain threshold and tolerated an objectively higher extent of pain.[30]

II. Diseases and clinical pictures occurring primarily in the brain

Since the very early stages of VNS, results have been observed in the treatment of depression and anxiety disorders.[31] Alongside this, there has also been MRI-documented evidence of an improvement in depressive moods, as well as a general elevation in mood, through the activation of corresponding brain areas.[32] Furthermore, studies have been carried out in the areas of ADHD and ADHD

[26] Rosenberg, p. 123 ff.; Straube et al., Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial, The Journal of Headache and Pain (2015) 16:63.

[27] Gaul/Magis/Liebler/Straube, Effects of non-invasive vagus nerve stimulation on attack frequency over time and expanded response rates in patients with chronic cluster headache: a post hoc analysis of the randomised, controlled PREVA study, Journal of Headache and Pain (2017) 18:22.

[28] Bonaz et al.: Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. Ed.: Neurogastroenterolog Motil. 2016, doi:10.1111/nmo.12792; Nesbitt et al.: Non-invasive vagus nerve stimulation for the treatment of cluster headache: a case series. The Journal of Headache and Pain 2013 1 (Suppl 1): P231.

[29] Gaul/Magis/Liebler/Straube, Effects of non-invasive vagus nerve stimulation on attack frequency over time and expanded response rates in patients with chronic cluster headache: a post hoc analysis of the randomised, controlled PREVA study, Journal of Headache and Pain (2017) 18:22.

[30] Laqua/Leutzow/Wendt/Usichenko, Transcutaneous vagal nerve stimulation may elicit anti- and pro-nociceptive effects under experimentally-induced pain — A crossover placebo-controlled investigation, Autonomic Neuroscience: Basic and Clinical 185 (2014) 120–122; Ness et al., Low Intensity Vagal Nerve Stimulation lowers human thermal pain threshold, Pain 86 (2000).

[31] Dr Scott Aaronson Am J Psych 2017; online 31 March; doi: 10.1176/appi.ajp.2017.16010034; Ellrich, Transcutaneous Vagus Nerve Stimulation, European Neurological Review, 2011;6(4): 254-6; Rosenberg, p. 156; Hein/Nowak/Kiess/Biermann/Bayerlein/Kornhuber /Kraus, Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study , J Neural Transm (2013) 120:821-827.

[32] Kraus/Hösl/Kiess/Schanze/Kornhuber/Forster, Bold fMRI deactivation of limbic and temporal brain structures and mood enhancing effects by transcutaneous vagus stimulation, J Neural Transmission (2007) 114: 1485 ff.

and autism[33] in connection with concentration disorders[34] with positive results. A reduction in aggressive behaviours has been observed in autistic patients. It is believed that this effect can be traced back to stimulation of the immune system. Here, stimulation was performed at 1-30 Hz.[35] tVNS also provides relief to patients with tinnitus, whereby stimulation of the part of the vagus nerve found in the ear (the auricular branch of the vagus nerve (ABVN)) is performed.[36] Finally, even improved memory retention has been observed under tVNS due to increased attention and relaxation[37]. Others observed supporting results in the cessation of smoking.[38]

III. Epilepsy

The entry point for VNS lies in the treatment of epileptic seizures. Several studies have evidenced antispasmodic effects[39] that are comparable with the effects of add-on epileptics.[40] In almost 30 per cent of patients, the frequency of seizures decreased by more than 50 per cent (response). Further positive effects on the state of health and quality of life have been observed thanks to good tolerability and the proven safety of the procedure.[41]

IV. Autoimmune system diseases

Considering the fundamental possibility of the vagus of settling a hyperactive immune system as well, there is positive evidence of VNS in relation to the supportive treatment of autoimmune system diseases. In this context, there have been observable results in terms of Crohn's disease[42] and rheumatoid arthritis[43].

[33] Rosenberg, P. 161, 163 ff.; Rush AJ et al.: Vagus nerve stimulation (VNS) for treatment-resistant depressions: A multicenter study. Biol Psychiat 2000; 47: 276-286.

[34] Rosenberg, p. 5.

[35] Jin/Kong, Transcutaneous Vagus Nerve Stimulation: A Promising Method for Treatment of Autism Spectrum Disorders, Frontiers in Neuroscience, January 2017/Volume 10/Article 609.

[36] Li et al., Transcutaneous electrical stimulation at auricular acupoints innervated by auricular branch of vagus nerve pairing tone for tinnitus: study protocol for a randomized controlled clinical trial, Trials (2015) 16:101.

[37] Jacobs/Riphagen/Razat/Wiese/Sack, Transcutaneous vagus nerve stimulation boosts associative memory
in older individuals, Neurobiology of Aging (2015) 1e8.

[38] Rosenberg, p. 4.

[39] Ellrich, Transcutaneous Vagus Nerve Stimulation, European Neurological Review, 2011;6(4): 254-6.

[40] Ben Menachem E: Modern management of epilepsy: Vagus nerve stimulation. Baillieres Clin Neurol 1996; 5: 841-848; Binnie CD: Vagus nerve stimulation for epilepsy: a review. Seizure 2000; 9: 161–169; Boon P, Vonck K, D'have M, O'Connor S, Vandekerckhove T, De Reuck J: Cost-benefit of vagus nerve stimulation for refractory epilepsy. Acta Neurol Belg 1999; 99: 275-280.

[41] Scherrmann/Hoppe/Kuczaty/Sassen/Elger, Vagusnerv-Stimulation: Neuer Behandlungsweg therapieresistenter Epilepsien und Depressionen [Vagus nerve stimulation: New treatment method for treatment-resistant epilepsies and depression disorders], Dtsch Arztebl 2001; 98(15).

[42] Douglas Fox, Can Zapping the Vagus Nerve Jump Start Immunity?, Nature, 04/05/2017.

[43] Thomas Ropp, How to Hack Your Nervous System, 05/09/2017

On the other hand, a general promotion of digestive activity[44] and in the supportive treatment of peripheral artery occlusion diseases[45] can be observed, linked to an effect of vagus nerve stimulation that tends to stimulate the immune and cardiovascular systems.

Finally, studies have nonetheless shown that tVNS also has a role in preventive healthcare through its strengthening of the body's own immune defences and increase in the ability to relax.[46] In relation to this, there is also an observed increase in melatonin secretion (the volume of the sleep hormone melatonin in the body) with a concomitant improvement in sleep and the body's ability to process sugar.[47]

E. Contraindications of tVNS and side effects

External vagus stimulation has very few side effects in general. No negative effects have been observed in studies.[48] Contraindications for stimulation include pacemakers, hearing aid implants and surgical transection of the vagus nerve. Irritation of the inner ear can also sometimes occur through stimulation.

F. Costs of vagus stimulation

VNS is typically not covered by statutory health insurers and is therefore subject to self-payment. Costs are partially covered by private health insurers and for those entitled to therapeutic care.

G. Use

Stimulation is carried out in the left ear as fewer undesired cardiac effects can be expected through this stimulation.[49] The electrode is positioned so that it incorporates the vagus running along the ear canal.[50]

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[44] Paulon E, et al., Proof of concept: short-term noninvasive cervical vagus nerve stimulation in patients with drugrefractory gastroparesis, Frontline Gastroenterology 2017;8:325-330. doi:10.1136/flgastro-2017-100809

[45] Hackl/Prenner/Jud//Hafner/Rief/Seinost/Pilger/Brodmann, Auricular vagal nerve stimulation in peripheral arterial disease patients, Vasa (2017), 46 (6), 462-470.

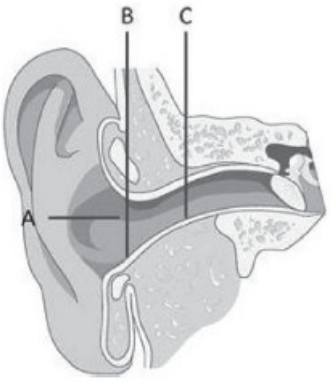
[46] Marca/Nedeljkovic/Yuan/Maercker/Ehlert, Effects of auricular electrical stimulation on vagal activity in healthy men: Evidence from a three-armed randomized trial, Zürich 2009.

[47] Wang S, Zhai X, Li S, McCabe MF, Wang X, Rong P (2015) Transcutaneous Vagus Nerve Stimulation Induces Tidal Melatonin Secretion and Has an Antidiabetic Effect in Zucker Fatty Rats, PLoS ONE 10(4): e0124195. poi:10.1371/journal. pone.0124195.

[48] On the example of the heart: Kreuzer/Landgrebe/Husser/Resch/Schecklmann/Geisreiter/Poeppl/Prasser/Hajak/Langguth, Transcutaneous vagus nerve stimulation: retrospective assessment of cardiac safety in a pilot study, Frontiers of Psychiatry, August 2012.

[49] Scherrmann/Hoppe/Kuczaty/Sassen/Elger, Vagusnerv-Stimulation: Neuer Behandlungsweg therapieresistenter Epilepsien und Depressionen [Vagus nerve stimulation: New treatment method for treatment-resistant epilepsies and depression disorders], Dtsch Arztebl 2001; 98(15).

[50] Bermejo/López/Larraya/Chamorro/Cobo/Ordóñez/



cavum conchae (A) and external (B) and internal (C)
[51]

The electrode is also moistened slightly with water or an electrode gel and then placed in the left ear, and finally the cable is placed around the ear for a better fit. Afterwards, connect the cable to your corresponding stimulator and start the stimulation. Adjust the intensity to a level that you find intense but not painful.

Vega, Innervation of the Human Cavum Conchae and Auditory Canal: Anatomical Basis for Transcutaneous Auricular Nerve Stimulation, BioMed Research International Volume 2017.

[51] Illustration from: Bermejo/López/Larraya/Chamorro/Cobo/Ordóñez/ Vega, Innervation of the Human Cavum Conchae and Auditory Canal: Anatomical Basis for Transcutaneous Auricular Nerve Stimulation, BioMed Research International Volume 2017.

Position the electrode on your left ear

Position the electrode in your left ear

Moisten the electrode with fresh water or an electrode gel

Feed the electrode cable around the left ear for better positioning

After the stimulation has finished, remove the electrode from the outer ear and clean it gently with warm water.

The stimulation should last approx. 20 minutes per use in the clinic or practice.

At home, stimulation should be carried out once or twice per day for approx. 20 minutes.

H. PROGRAMME RECOMMENDATIONS

Transcutaneous vagus nerve stimulation (tVNS) can be carried out using multiple stimulators. The AS SUPER 4 Digital, which lets you make fine adjustments to the intensity, should come under consideration for clinics and practices in particular. Stimulation at home is feasible with the TENS-TEM ECO, ECO Basic, ECO 2 or also the Omni-TENS-XP.

Different recommendations on the choice of frequencies can be found in the literature:

- low-frequency pulses should be used accordingly to reduce blood pressure and for a resulting, generally relaxing effect, while high-frequency pulses are instead intended to cause a stimulation in blood pressure.[52]

- In stimulation against migraine,[53] significantly better results were achieved in the treatment of headache when utilising 1-3 Hz stimulation, with a reduction in headache attacks of > 50% vs > 13%.[54]

- For autism, a reduction in aggressive behaviours has been observed. It is believed that this effect can be traced back to stimulation of the immune system. Here, stimulation was performed at 1-30 Hz.[55]

- A reduction in aggressive behaviours has been observed in autistic patients. It is believed that this effect can be traced back to stimulation of the immune system. Here, stimulation was performed at 1-30 Hz.[56]

[52] Sartori/Stein/Coronel/Edler/Della Méa Plentz, Effects of Transcutaneous Electrical Nerve Stimulation in Autonomic Nervous System of Hypertensive Patients: A Randomized Controlled Trial, Current Hypertension Reviews, 2018, 14, 66-71.

[53] Goadsby/Grosberg/Mauskop/Cady/Simmons, Effect of noninvasive vagus nerve stimulation on acute migraine: An open-label pilot study, Cephalalgia 2014, Vol. 34(12) 986-993.

[54] Rosenberg, p. 123 ff.; Straube et al., Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial, The Journal of Headache and Pain (2015) 16:63.

[55] Jin/Kong, Transcutaneous Vagus Nerve Stimulation: A Promising Method for Treatment of Autism Spectrum Disorders, Frontiers in Neuroscience, January 2017/Volume 10/Article 609.

[56] Jin/Kong, Transcutaneous Vagus Nerve Stimulation: A Promising Method for Treatment of Autism Spectrum Disorders, Frontiers in

- For epilepsy, however, stimulation was typically carried out at 25 Hz[57]

- For tinnitus, stimulation was carried out at 25 Hz in 1-2 sessions per week for over approx. 30 minutes[58]

For stimulation using TENS ECO, stimulation should be carried out using programmes 3, 8 or 10.

For stimulation using TENS ECO Basic, stimulation should be carried out using programmes 3, 8 or 10.

For stimulation using TENS ECO 2, stimulation should be carried out using programmes 3, 8 or 10 or U 10.

For stimulation using AS SUPER 4, stimulation should be carried out using programmes 1, 2, 5 or 9.1 and 9.4.

For stimulation using Omni TENS XP, stimulation should be carried out using programmes 1, 3 or 8.

I. Distribution

Vagus nerve electrodes can be obtained from schwa medico GmbH under item no. 107065. Orders can be placed by telephone on +49 (0)64438333110, by email at info@schwa-medico.de or by post to schwa medico GmbH, Wetzlarerstr. 41-43, 35630 Ehringshausen, Germany.

Neuroscience, January 2017/Volume 10/Article 609.

[57] Bauer/Baier/Baumgartner/Bohlmann/Fauser/Graf/Mayer/Schulze-Bonhage/Steinhoff/Weber/Rosenow/Hamer, Transcutaneous Vagus Nerve Stimulation (tVNS) for Treatment of Drug-Resistant Epilepsy: A Randomized, Double-Blind Clinical Trial, Brain Journal 2016.

[58] Tian-Tian Li (2015) "Transcutaneous electrical stimulation at auricular acupoints innervated by auricular branch of vagus nerve pairing tone for tinnitus: study protocol for a randomized controlled clinical trial", Trials, vol. 16, p. 101. • Hoare et al. Electrical Stimulation of the Ear, Head, Cranial Nerve, or Cortex for the Treatment of Tinnitus: A Scoping Review. Neural Plasticity. Volume 2016, Article ID 5130503, 15 pages • Lee et al. (2014). Effectiveness of transcutaneous electrical stimulation for chronic tinnitus, Acta OtoLaryngologica, 134:2, 159-167 • Hyun Joon et al. Feasibility and Safety of Transcutaneous Vagus Nerve Stimulation Paired with Notched Music Therapy for the Treatment of Chronic Tinnitus. J Audiol Otol 2015;19(3):159-167 • De Ridder et al. Placebo-controlled vagus nerve stimulation paired with tones in a patient with refractory tinnitus: a case report. Otol Neurotol. 2015 Apr.; 36(4):575-80. • Hyvärinen et al. Transcutaneous Vagus Nerve Stimulation Modulates Tinnitus-Related Beta- and Gamma-Band Activity. Ear & Hearing 2015;36:e76-e85 • Lehtimäki et al (2013) Transcutaneous vagus nerve stimulation in tinnitus: a pilot study, Acta Oto-Laryngologica, 133:4, 378-382.

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