

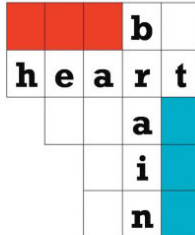


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Vagal functionality as indicator for biopsychological stress responsiveness and beneficial effects of auricular electrical stimulation on vagal activity

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 Cuvillier Verlag Göttingen
Internationaler wissenschaftlicher Fachverlag

<https://cuvillier.de/de/shop/publications/1030>

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Telefon: +49 (0)551 54724-0, E-Mail: info@cuvillier.de, Website: <https://cuvillier.de>

2.1.1.2 The peripheral autonomic nervous system

The cell bodies of preganglionic neurons of the peripheral ANS lie in the central nervous system (CNS). The short sympathetic preganglionic fibers leave the spinal cord to the near chain of sympathetic ganglia and activate long, unmyelinated postganglionic nerve fibers through chemical cholinergic synapses. Postganglionic neurons principally release norepinephrine (NE). By contrast, the PNS mediates its effects by leaving the CNS, among others, out of the brain stem through cranial nerves containing long and in part myelinated preganglionic fibers. The PNS releases acetylcholine (ACh) in the parasympathetic ganglions situated near to or in the walls of the target organs, where in contrast to the SNS, they release ACh (Birbaumer & Schmidt, 2003).

The ANS adapts the processes of the body to the rapidly changing demands of the environment and coordinates two major roles: homeostasis and the adaptive responses to stress (fight-or-flight response). To fulfil these two functions, it can fall back on the mostly antagonistic functions of the SNS and PNS on most of the innervated organs (tab. 2.1).

Table 2.1 Functions of the ANS (Hamill & Shapiro, 2004)

| Organ | SNS | PNS |
|---------------------------|------------------------------------|------------------------------------|
| Eye (pupil) | Dilation | Constriction |
| Eye (ciliary muscle) | Relax (far vision) | Constrict (near vision) |
| Lacrimal gland | Slight secretion | Secretion |
| Parotid gland | Slight secretion | Secretion |
| Submandibular gland | Slight secretion | Secretion |
| Heart | Increased rate; pos. Inotropism | Slowed rate; neg. inotropism |
| Lungs | Bronchodilation | Bronchodilation |
| Gastrointestinal tract | Decreased motility | Increased motility |
| Kidney | Decreased output | - |
| Bladder | Relax detrusor; contract sphincter | Contract detrusor; relax sphincter |
| Penis | Ejaculation | Erection |
| Sweat gland | Secretion | Palmar sweating |
| Piloerection muscles | Contraction | - |
| Blood vessels: arterioles | Constriction | - |
| Muscle (arterioles) | Constriction or dilation | - |
| Muscle (metabolism) | Glycogenolysis | - |

2.1.2 The vagus nerve

The VN (X. cranial nerve) constitutes the main portion of the PNS, innervates a multitude of organs and is vitally important (Benninghoff, 2008). It contains visceromotoric, viscerosensoric, and somatosensitive nerve fibers (Trepel, 2004), while the viscerosensitive afferents constitute 80% of the vagal fibers (Porges, 2003). The fibers of the VN are associated with four interconnected nuclei: the DMN contains visceromotor nerve fibers innervating among others the heart and lung, the NA contains visceromotor nerve fibers innervating organs superior to the thoracic diaphragm, the nucleus spinalis nervi trigemini (NSNT) receiving somatosensitive afferents and the NTS receiving viscerosensitive input and afferent information from the N. glossopharyngeus, N. facialis, and the NSNT (Chien et al., 1996; Trepel, 2004). The NTS, as mentioned above, possesses a multitude of direct and indirect connections to the other structures of the CAN. The VN leaves the brain stem behind the olive and extends through the foramen jugulare in the skull to the head, neck, chest and abdomen (Trepel, 2004) and divides into several branches. In general, the VN is involved in digestive and restorative somatic function (Swanson, 2003).

2.1.2.1 Vagal innervation of the heart

Two branches, the rami cardiaca cervicales superiores and inferiores, quit the DMN to innervate the plexus cardiacus of the heart. The right rami of the bilaterally organized VN mainly connects with the sinoatrial node, while the left rami innervate mainly the atrioventricular node. Conversely, viscerosensitive afferents reach the NTS through the same rami (Trepel, 2004). The heart is innervated by both branches of the ANS, which at the plexus cardiacus constitutes the major modulator of heart activity (Cacioppo, Tassinari & Berntson, 2007). The heart is active per se, since it contains cardiac myocytes and some of them are

subsumed in the sinoatrial node functioning as a pacemaker (Thews & Vaupel, 2005). The heartbeat of the denervated heart has a pace of about 100 beats per minute (bpm; Ganong, 2005; cited after Chai et al., 2008, p. 695), while sympathetic innervation produces an increase and vagal innervation a decrease of the heart rate (HR) (Cacioppo et al., 2007). However, an increase of HR can also be produced by a reduced vagal activation. As described by Thayer and Lane (2009), the increase of HR can be initiated in the CAN (fig. 2.8). The bidirectional and interacting forebrain structures can activate sympathoexcitatory neurons of the rostral ventrolateral medulla (RVLM), therefore increasing HR. But the structures of the CAN can simultaneously inhibit the NTS, thereafter eliciting a decreased activity of the visceromotor neurons in the DMN and NA, which results in a reduced vagal input to the heart leading to an increase in HR. Additionally, a CAN-mediated reduced activation in the NTS leads to a decrease of inhibition on the sympathoexcitatory neurons of the RVLM, again eliciting an increase in HR.

The normal contraction rate of 72 bpm at rest (Andrassy, 2007) compared to the 100 bpm in a denervated heart, underlines the dominance of the vagal input to the heart. In general, the VN possesses a negative chronotropic, dromotropic, and inotropic effect, resulting in a decrease in HR, an increase in time of intracardiac signal transmission, and a decrease in contractility (Lewis et al., 2001; Thews & Vaupel, 2005). An important difference between vagal and sympathetic innervation characteristics is the kinetics. While vagal inputs effect and decay rapidly and within a heartbeat, sympathetic inputs are much slower (Franchini & Cowley, 2004; Spear et al., 1979).

The bidirectional connection between the brain and the heart plays an important functional role in the fight-or-flight response but also in emotional, cognitive and attentional regulation. Vagal tone, further to be an output variable, can additionally be seen as a resource of the individual in a challenging environment (Thayer & Lane, 2009).

Although the main factor influencing cardiac activity is the impact of autonomic innervation described above, several other factors can influence the activity of the heart. Some of the most prominent factors controlling the heart besides the direct autonomic innervation are neuropeptides (for example neuropeptide Y (NPY), which is often present in autonomic synapses), indirect autonomic influence through catecholamines predominantly secreted after activation of the sympatho-adrenomedullary (SAM) system, activity alterations of the renin-angiotensin system (RAS), and the respiratory-related mechanical stretch of the sinoatrial node (Berntson et al., 1997).

2.1.2.2 Vagal innervation of the ear

The ear is an important organ, among other things in social interaction or in the detection of the direction of auditory threat signals. However, it is not a vital organ, but since the ear and its innervation plays a crucial role in the present work, the neuroanatomical basis of the ear is nevertheless presented. The ear is innervated among other things by the VN (Fallgatter et al., 2003; Lang, 1992; Tekdemir et al., 1998). The auricular branch of the VN, the ramus auricularis nervi vagi, is also called the Alderman's or Arnold's nerve. The Arnold's nerve contains vagal afferents leading from the skin of the external auricular canal (external acoustic meatus), through the fissura tympanomastoidea and the mastoidal canal into the superior ganglion, relaying the information through the foramen jugulare into the NSNT (Benninghoff, 2008). However, afferents are also reported in the concha (Lang, 1992), and there is additional evidence for vagal afferents in the helix and antihelix of the ear (Gao et al., 2008) and the presence of heterogeneous nerve fibers in one and the same area (Folan-Curran & Cooke, 2001).

The NSNT projects to the NTS (Chien et al., 1996), which leads bottom-up information to the structures of the CAN and might also influence affective state (Kraus et al., 2007). However,

together with the NSNT, the NTS can also interact with the visceromotor vagal nuclei, integrating these inputs with top-down information affecting cardiac function. The NSNT was shown to elicit a bradycardia and a hypotension in rabbits during electrical stimulation of the NSNT (Kumada et al., 1977). After several adjuvant pharmacological and surgical interventions, the authors came to the conclusion that the stimulation of the NSNT leads to a reflex activating cardiovagal efferents and an inhibition of cardiosympathetic nerve fibers, while baroreceptors do not seem to be too affected. The authors report that this reflex can be elicited through the stimulation of different cranial nerves such as the N. trigeminus (V.), the N. glossopharyngeus (IX.) and the somatosensitive nerve fibers of the NV (X.). Therefore, the stimulation of the ear, but also the reflex mediated through application of a cold stimulus like in the CFT, are thought to be mediated at least among other things through the stimulation of the NSNT. Aside from bradycardia as part of the diving reflex, stimulation of the ear can provoke different reflexes such as ear-palatal and the ear-vomiting reflexes attributable to vagal stimulation (Gupta et al., 1986; Majer, 1953).

2.1.2.3 Indicators of vagal activity: markers not referring to the heart

The PNS innervates several organs affecting their activity by some means or other. Normally, the innervated organs have several influencing factors and therefore their activity cannot uniquely be linked to parasympathetic input. Nevertheless, they provide some information on the activity of the PNS.

Pupillary responses are frequently used indicators of autonomic state. Alterations of the pupillary aperture are mediated through the ANS. While the SNS leads to a dilation of the pupil through activation of the radial fibers, the PNS leads to a pupillary constriction through innervation of circular fibers of the iris (Andreassi, 2007). This latter response is indicative of

the activity of the parasympathetic efferents along the III. cranial nerve (oculomotor nerve), but might not be associated with the activity of the VN.

The VN innervates, among others, the thyroid gland, thymus and pancreas. In these organs, vagal stimulation can alter the secretion of several substances. In the thyroid gland, vagotomy and stimulation studies suggest, among other things, a positive association between vagal activity and the secretion of calcitonin gene-related peptide (CGRP; Grunditz et al., 1986), substance P (Grunditz et al., 1988), and vasoactive intestinal peptide (VIP; Ito et al., 1987) and an inhibitory influence of the VN on thyroid hormone secretion (Melander et al., 1979). Referring to the thymus, the VN is thought to heighten lymphocyte release (Antonica et al., 1994). In the pancreas, the vagal stimulation can increase the secretion of amylase (Vega et al., 1977), while 2-3 months after a vagotomy, pancreatic gland weight and the amount of Langerhans islets were found to decrease (Tiscornia et al., 1981). The latter are important for the release of insulin and amylin.

These findings are only a small selection of the effects of the VN on the body. The problem about these parameters is that they can only be measured invasively and are susceptible to many influencing factors. Therefore, the markers above can indicate the state of the VN, but due to the many influencing factors cannot be seen as proper marker of vagal activity. Measuring vagal activity markers associated with cardiac and cardiorespiratory activity seems to be much more useful and reliable, since alterations of these markers allow a clearer attribution to vagal state and since a continuous measurement is possible.

2.1.2.4 Indicators of vagal activity: electrocardiographic markers

When considering the heart, several measures are used to indicate vagal activity. Electrocardiac markers thereby hold a great advantage compared to the determination of the non-cardiac markers mentioned above: the simplicity of determination, since electrocardiac

markers can be measured non-invasively on the body surface with stationary but also small and easy-to-wear ambulatory devices. Therefore, subjects can be examined in nearly every situation all day long.

All cardiac markers discussed in the following rely on the electrocardiogram (ECG). The early measurement of heart activity took place with galvanometers around 1900. The underlying phenomenon is based on the fact that a part of the electrical impulses passing the heart during its contraction spreads to the body's surface and can therefore be detected by electrodes on the skin. Thus, the ECG is the record of amplified cardiac electrical potentials on body surface. The ECG shows several signal alterations (fig. 2.2).

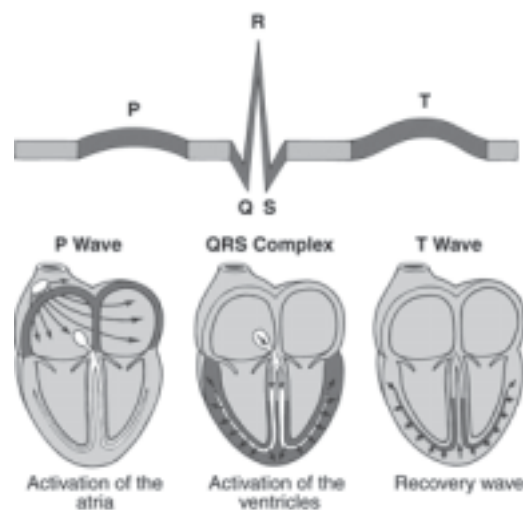


Figure 2.2 Electrocardiogram (reproduced with permission from Porter, 2003, available:

http://www.merck.com/media/mmhe2/figures/MMHE_03_021_01_eps.gif)

The most important ones determine the QRS complex, representing currents generated in the ventricles (fig. 2.2) during depolarization prior to ventricular contraction. The P wave refers to the current generated before the contraction of the atria and the T wave the repolarisation of the ventricles (Andreassi, 2007).

For psychophysiological research, the most interesting characteristic extracted from the ECG is the RR interval (or NN interval; interval between two R waves). The time in-between two beats is called heart period (HP) or inter-beat-interval (IBI). Based on the HP, the heart rate (HR) can be reciprocally determined. In fact, the HR is based on the number of beats per unit of time (normally per one minute), and can therefore be determined with the following formula (Vossel & Zimmer, 1998): $HR \text{ (bpm)} = 60'000 \text{ (ms)} / HP \text{ (ms)}$.

Besides variations of HR called heart rate variability (HRV; see below), resting HR can be interpreted as an index of vagal activity, since under resting conditions, the heart is under predominant vagal inhibition (Thayer & Sternberg, 2006). Additionally, the HR change after cessation of physical exercise, called HR recovery, is used as an index of vagal activity (Thayer & Lane, 2007). An alternative and more complex variable is HRV, which offers the basis for several markers indicating the state of the ANS. At the beginning of cardiophysiological research, HR was thought to be a stable rhythm. As noted by Porges (2007), in the past, HRV was often misleadingly interpreted by several prominent psychophysiologicalists as an artefact due to poor experimental control. However, some authors noticed the simplest detectable marker of HRV early on: the alterations of HR in association with respiration. Hales (1733; cited following Berntson et al., 1997) was one of the first researchers to observe a respiratory pattern in the pulse and blood pressure of a horse. The alteration in the pulse associated with breathing is called respiratory sinus arrhythmia (RSA; fig. 2.3).