Autonomic nervous system function and behavioral characteristics in (pre)adolescents from a general population cohort

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THE AUTONOMIC NERVOUS SYSTEM

CHAPTER

2

Function and structure

The autonomic nervous system is concerned with the regulation of the circulation and the body's internal environment (Despopoulos *et al.* 1991). The autonomic system has thus a clear homeostatic function and is therefore of vital importance for the well-being of the organism (Stern *et al.* 2000). In general, it controls activities that are not under voluntary control, thus functioning below the level of consciousness. Functions are, for example, regulation of respiration, digestion, body temperature, and metabolism. The heart and the circulation are central target organs or functions. The sympathetic and the parasympathetic nervous systems are the two main branches of the autonomic nervous system. The anatomic centers of the sympathetic division lie in the thoracic and lumbar levels of the spinal cord, and those of the parasympathetic division lie in the brain stem (eyes, glands, and organs innervated by the vagus nerve) and sacral part of the spinal cord (Despopoulos *et al.* 1991) (figure 1).

Sympathetic nervous system

The sympathetic nervous system helps mediate vigilance, arousal, activation, and mobilization, and prompts bodily resources to cope with increased metabolic needs during challenging situations (Sapolsky 1998). The sympathetic system normally is continuously active; the degree of activity varies from moment to moment (Stern *et al.* 2000). However, during emergencies or threat, activity of the sympathetic nervous system comes to a maximum. The sympathetic division is thus closely linked to the *fight-or-flight response*, also called the *acute stress response*, which triggers rises in respiration, heart rate (HR), and blood pressure (BP).

Parasympathetic nervous system

The parasympathetic nervous system is primarily concerned with the conservation of energy and maintenance of organ function during periods of minimal activity (Stern *et al.* 2000). Further, it promotes restoration of health following threats or challenges (Porges *et al.* 1996). The parasympathetic division is sometimes called the *rest and digest system*. In contrast to the sympathetic nervous system, the parasympathetic system is organized mainly for discrete and localized discharge and is rapid and reflexive in nature (Stern *et al.* 2000). For example, during stressful situations, the parasympathetic system generally retracts itself quickly to facilitate adaptation to environmental demands (Porges 1995). This does, however, not exclude a constant flow of parasympathetic activity, which is illustrated by the fact that intrinsic HR would be well over 100 beats per minute without parasympathetic influences, instead of an average of 70 beats per minute normally observed. Thus, the parasympathetic system slows the HR and also lowers the BP. The vagus nerve is the most important anatomic structure by which the parasympathetic nervous system exerts its influence, hence the term vagal is used synonymous with parasympathetic.
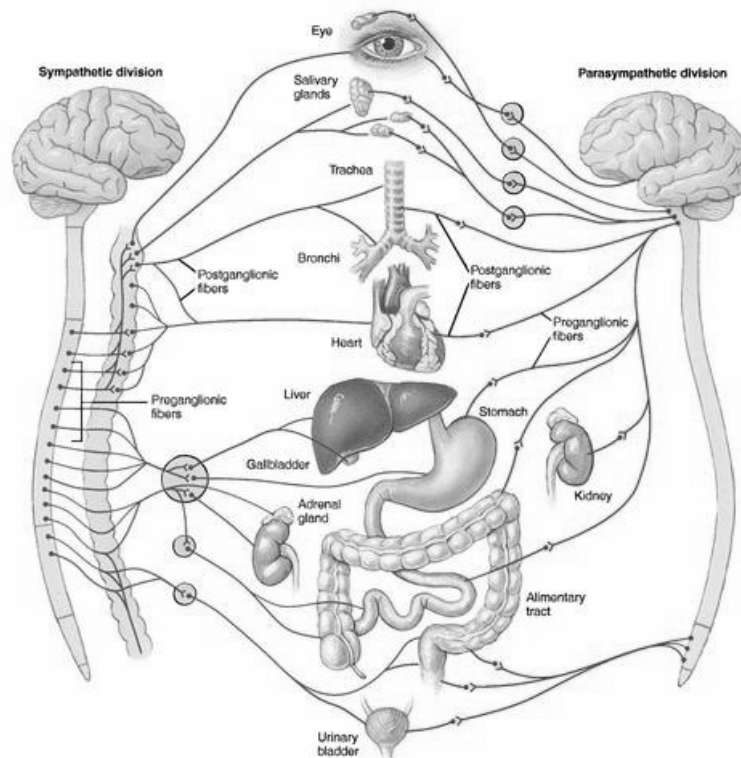
Figure 1. The sympathetic and parasympathetic branches of the autonomic nervous system.

Modes of function - Autonomic space

Traditionally, the sympathetic and parasympathetic branches have been regarded as acting in an opposite (antagonistic or reciprocal) manner. By now, it has become clear that this is an oversimplification and that both systems may be concomitantly active (coactivation) or operate independently of each other (uncoupling) (Hughdal 2001). The different modes of autonomic control of the sympathetic and parasympathetic divisions have been described in a model on autonomic space (Berntson *et al.* 1991) (figure 2).

		Parasympathetic Activity		
		Parasympathetic Activation	No Change	Parasympathetic Withdrawal
Sympathetic Activity	Sympathetic Activation	Coactivation	Uncoupled Sympathetic Activation	Reciprocally Coupled
	No Change	Uncoupled Parasympathetic Activation	No Change	Uncoupled Parasympathetic Withdrawal
	Sympathetic Withdrawal	Reciprocally Coupled	Uncoupled Sympathetic Withdrawal	Coinhibition

Figure 2. Modes of autonomic function (by Berntson, Cacioppo, and Quigley, 1991).

Measures of the autonomic nervous system

HR is probably the most investigated and readily assessable measure of autonomic function in psychophysiological research. It reflects the balance between activity of the sympathetic and parasympathetic autonomic nervous system. As such, it is not a specific measure of underlying autonomic function, although it may be inferred that parasympathetic activity predominates during resting conditions and sympathetic activity during stimulated situations (Jose 1966, Pomeranz *et al.* 1985).

A technique that has been frequently applied to gain more insight into autonomic regulation is spectral analysis using fast Fourier transformations, which converts a signal in the time domain, such as beat-to-beat HR and BP, to a signal in the frequency domain (Akselrod *et al.* 1981). Frequency is defined as the number of oscillations per second (in Hertz, Hz, meaning 'per second'). As an example, a frequency of 0.2 Hz corresponds with 12 cycles or periods within 60 seconds, with a duration of 5 seconds each period (figure 3).

It is well-known that HR and BP are constantly changing (Karemaker 1993). These variations of HR or BP in time (i.e., changing inter-beat intervals), derived from a continuous electrocardiogram or BP measurement, can be set out in a tachogram (figure 4). Analysis of this waveform identifies the underlying rhythms as a combination of sine and cosine waves of various amplitude, frequency, and phase (figure 5). The output of a spectral analysis is the squared magnitude of the Fourier transform and is typically graphed as a curve showing the strength, or power (amplitude), of the frequencies into which the original signal can be decomposed (this is also called the power densitiy spectrum, figure 6) (Stern *et al.* 2000). Thus, spectral analysis partitions the total variance in HR or BP into underlying periodic rhythms that occur at different frequencies, which are supposed to reflect different physiological processes.

The HR spectrum commonly describes the power in the ultra low and very low frequency band (ULF, VLF, below 0.04 Hz, fewer than 2.4 cycles per minute), low frequency band (LF, 0.04-0.15 Hz, between 2.4 and 9 cycles per minute), and high frequency band (HF, 0.15-0.40 Hz, between 9 and 24 cycles per minute) (Akselrod *et al.* 1981, Pomeranz *et al.* 1985).

The physiological source of the ULF and VLF is poorly understood; in addition to autonomic influences, thermoregulatory and metabolic processes have been mentioned (Stern *et al.* 2000). These frequencies are not considered in our study, since only short recordings of about 2 to 4 minutes have been assessed.

In the HR variability spectrum, two prominent peaks are observed, at about 0.1 Hz (the low frequency peak) and 0.25 Hz (the high frequency peak) (figure 6). The 0.1 Hz peak can also be found in the BP variability spectrum (Karemaker 1993). Variability in the 0.1 Hz component primarily originates from variations in BP related to sympathetic tone, which is regulated by the sympathetic and parasympathetic arms of the baroreflex (discussed later in more detail). Thus, the LF band mediates sympathetic as well as parasympathetic activity (Pomeranz *et al.* 1985).

The HF band, on the other hand, is primarily linked to respiration and almost exclusively determined by parasympathetic activity (Berntson *et al.* 1993, Saul *et al.* 1991). The oscillatory influence of respiration on HR has been referred to as respiratory sinus arrhythmia (RSA) (Stern *et al.* 2000). Inspiration inhibits vagal outflow and increases HR, whereas expiration disinhibits vagal outflow and decreases HR. Over the past decade, RSA has received much attention in psychophysiology research as a noninvasive index of vagal control (Stern *et al.* 2000).

In this thesis, the time domain measures HR and systolic BP have been included, as well as the spectral measures HRV in the low frequency band (HRV-LF) and the high frequency band (HRV-HF or RSA), and BPV in the low frequency band. Also, baroreflex sensitivity (BRS) has been investigated, which is described in the following paragraph.
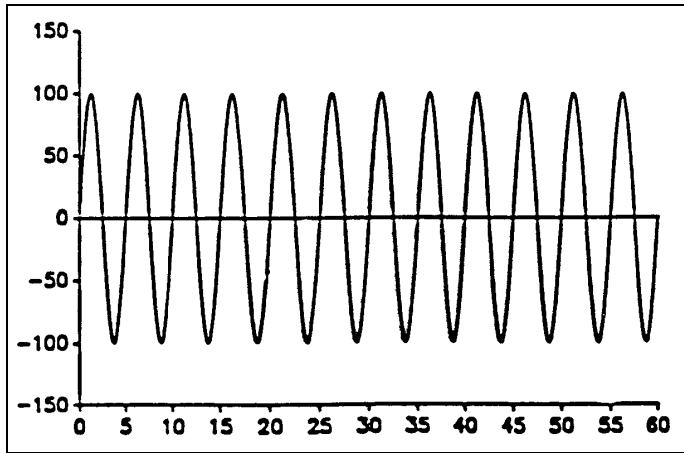
Figure 3. Number of cycles per minute. A frequency of 0.2 Hz corresponds with 12 cycles or periods within 60 seconds.
(From: Phyllis K. Stein, Washington University School of Medicine, St. Louis.)
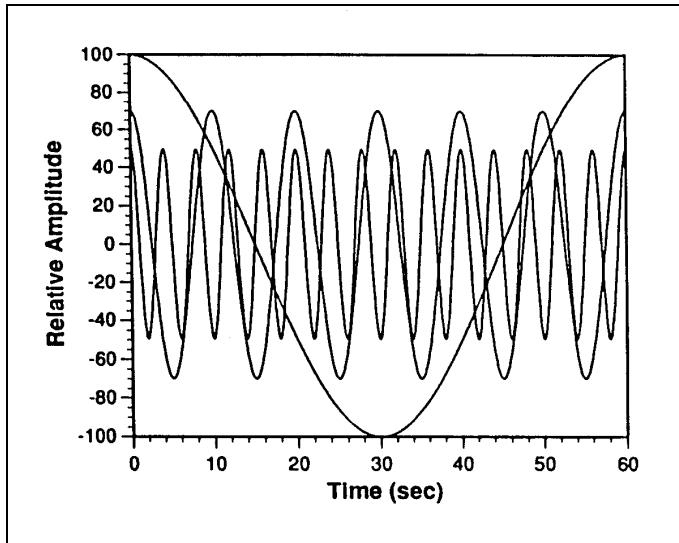

Figure 5. Waves of three rhythms (very low frequency 0.016 Hz or 1 cycle/min; low frequency 0.1 Hz or 6 cycles/min; high frequency 0.25 Hz or 15 cycles/min).
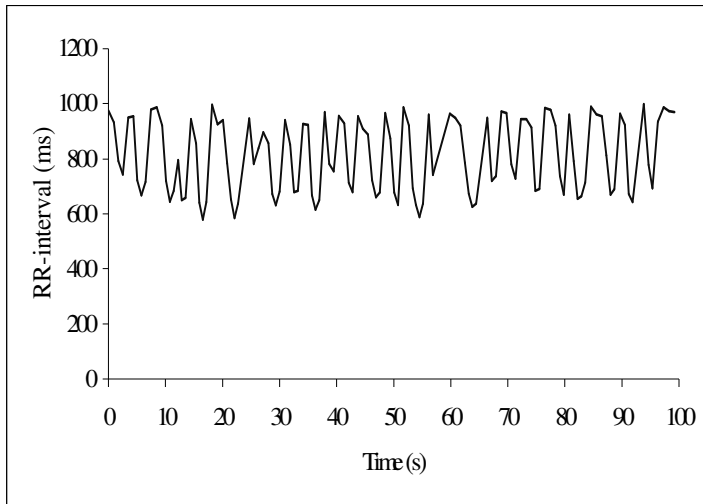*(From: Phyllis K. Stein, Washington University School of Medicine, St. Louis.)*

Figure 4. Tachogram of RR-interval (ms) of one individual.
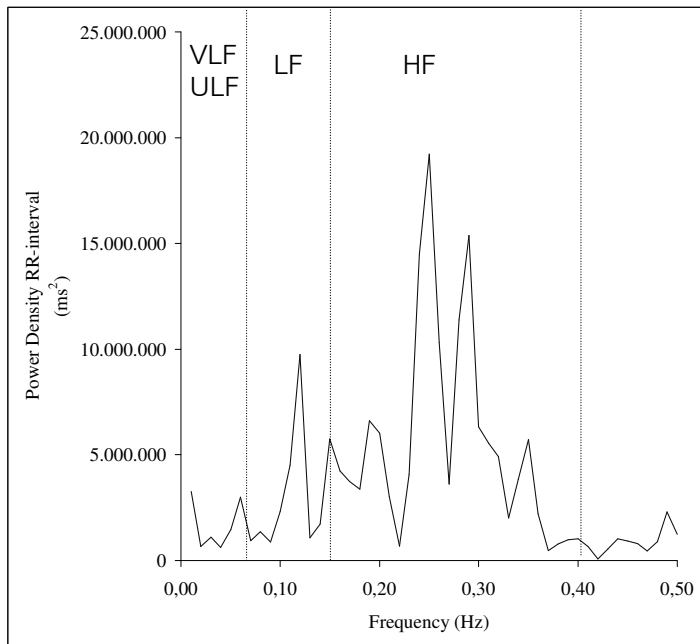The R-peak is the most prominent peak in an electrocardiogram.

Figure 6. Power density spectrum of RR-interval (ms^2) of one individual.
ULF=ultra low frequency, VLF=very low frequency, LF=low frequency,
HF=high frequency.

Baroreflex sensitivity

The baroreflex is an important short-term BP control mechanism (Ketch *et al.* 2002) and functions as a negative feedback loop: based on afferent information of arterial baroreceptors reacting on changes in BP, central cardiovascular control is exerted on different peripheral effector systems (i.e., HR, cardiac output, contractility of heart, peripheral resistance) to keep BP between narrow limits. Thus, pressure-sensitive baroreceptors, most of which are located in the aorta and carotid sinus, react on stretch or deformation of blood vessels associated with BP changes. Afferent nerve fibers transmit this information to the cardiovascular control center in the medulla oblongata in the brain stem, which in turn controls efferent sympathetic and parasympathetic nerve fibers to the heart (sympathetic and parasympathetic) and vasculature (only sympathetic). The baroreceptor reflex pathways and cardiovascular control center are described in more detail in figure 7a.

The beat-to-beat function of the baroreflex is illustrated in figure 7b. As an example, when BP elevates, baroreceptor firing and afferent carotid sinus nerve impulses will increase, consequently efferent vagal nerve impulses will increase and/or sympathetic nerve impulses decrease, such that HR will be slowed, which will finally result in a decrease of BP. In an opposite fashion, when BP reaches lower than normal levels, baroreceptor firing and afferent carotid sinus nerve impulses will decrease, consequently efferent vagal nerve impulses will decrease and/or sympathetic nerve activity will increase, such that HR will be fastened, which will finally result in an increase of BP.

BRS is commonly defined as reflecting variations in beat-to-beat HR resulting from variations in systolic BP and is an integrated measure of both sympathetic and parasympathetic activity. In our studies, spectral analysis was used to calculate BRS, based on the transfer function between HR variability and BP variability in the low frequency band. Three calculations are gained, the modulus (BRS value), coherence and phase. The coherence reflects the amount of variance in HR as a result of changes in BP. The phase describes the time delay between the HR and BP spectra. A BRS of 10 ms/mmHg indicates that a rise of 1 mmHg in systolic BP induces a lengthening of 10 ms of the interval between two heart beats (i.e., RR-interval). A reduced BRS is a well-known indicator of autonomic dysfunction (Gerritsen *et al.* 2001, La Rovere *et al.* 1998).
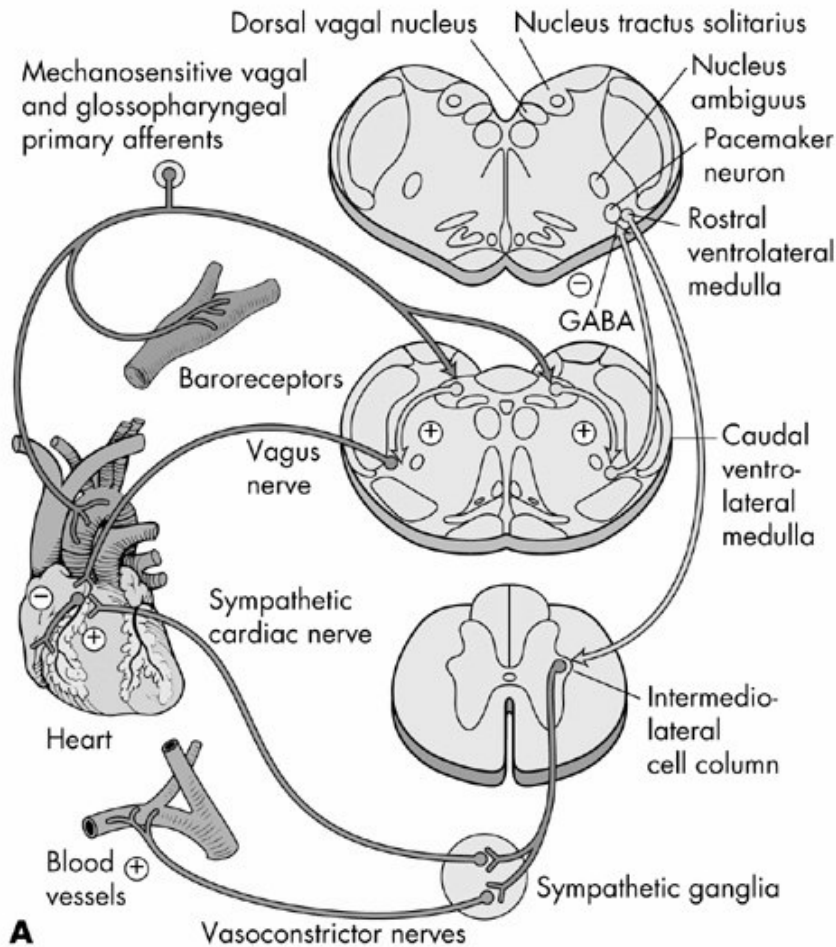
Figure 7a. Baroreceptor reflex pathways and autonomic nervous system control center.

a. Primary afferent fibers arising from high-pressure mechanosensory endings in the heart, aorta, and carotid sinus project within the vagal and glossopharyngeal nerves to the nucleus tractus solitarius (NTS). Excitatory NTS outputs project to the vagal motor nucleus (nucleus ambiguus) and to the caudal ventrolateral medulla (CVM), activating an inhibitory (GABAergic) interneuron relay to the rostral ventrolateral medulla (RVM). Efferent limbs completing negative feedback loops consist of (inhibitory) vagal projections to the heart and sympathetic efferent projections from the RVM to the heart and vasculature via the interomedial column of the spinal cord (IML) and sympathetic ganglia. Heart rate reflex responses to changes in arterial pressure are determined by the balance between vagal and sympathetic efferent cardiac nerve activities. Reflex changes in systemic vascular resistance are determined by changes in vasoconstrictor nerve activities.
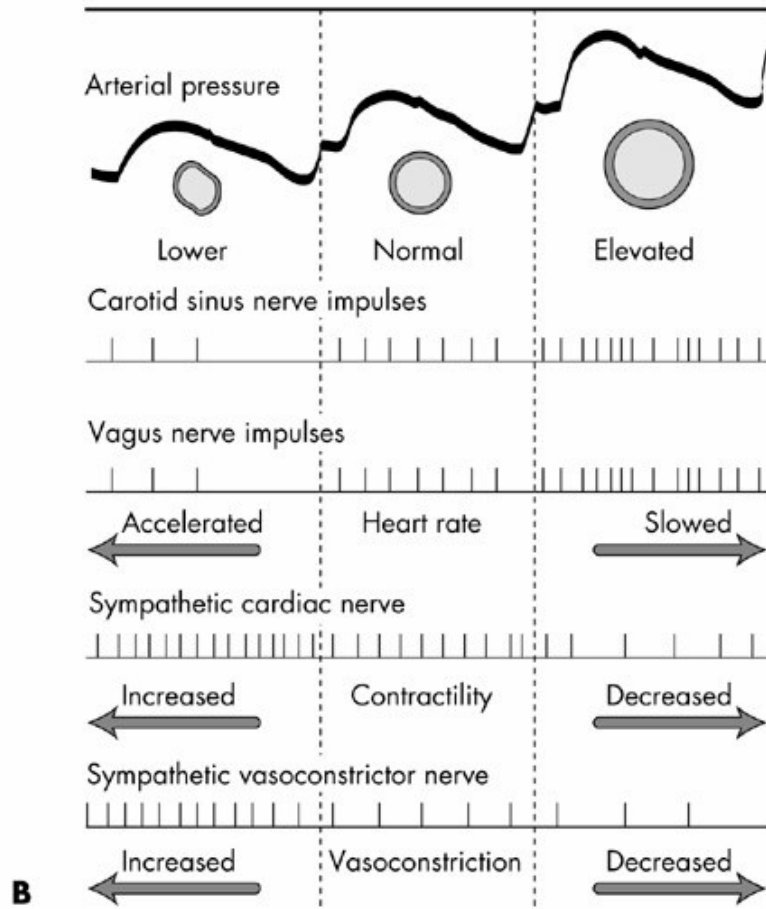
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Figure 7b. Beat-to-beat function of the baroreceptor reflex.

b. Changes in arterial blood pressure result in parallel changes in the firing rate of carotid sinus nerve afferent impulses. These changes in the afferent nerve firing rate, in turn, cause parallel changes in vagal efferent and reciprocal changes in sympathetic efferent nerve firing rates.

(From: Stapelfeldt W., Atlas of Anesthesia: Scientific Principles of Anesthesia. Edited by Ronald Miller, Debra A. Schwinn, Current Medicine, Inc., 1997).

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