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Review

Heart rate variability (HRV): From brain death to resonance breathing at 6 breaths per minute

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HIGHLIGHTS

- Heart rate variability (HRV) is sensitive to central nervous system function.
- Findings from extreme clinical conditions illustrate brain–heart interactions.
- Organismic oscillatory activity could play a major role in mental and physical health.

ABSTRACT

Heart rate variability (HRV) has been associated with various diseases and reflects autonomic cardiac control sensitive to central nervous system function. Examples of the heart-brain interaction are illustrated by extreme clinical conditions such as brain death, orthotopic heart transplantation, weaning from respirator support, and brain maturation in preterm infants. Interactions with the immune system document the importance of HRV for tumor growth and prognosis. Research linking HRV to the regulation of negative emotions including depression and anxiety document the sensitive influence of central commands on cardiac activity. Moreover, 0.1 Hz oscillations in the heart and the brain seem to be coupled, thus indicating central pacemakers on the heart rhythm. Moreover, low frequency oscillations in heart rate seem to be composed of two subcomponents presumably signaling different central-autonomic functions. We conclude by showing that breathing at 6 breaths/minute could induce coherence of the 0.1 Hz oscillations, thus facilitating physical and psychological function. The reviewed findings impressively demonstrate that central nervous system function modifies the rhythm of the heart and vice versa, suggesting that HRV could be a useful indicator of central-autonomic integration and that 0.1 Hz oscillations play a major role in physical and mental health via optimizing energy supply.

Contents

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1. Introduction

Heart rate variability (HRV) reflects the variation of the inter-beat intervals of the heart (so-called RR-intervals) and is considered to reflect the organism's capacity to adapt to changes of endogenous and exogenous influences to match the needs of blood supply (Thayer et al., 2012). The analysis of HRV is therefore of increasing interest in various fields of research. HRV can be used as a biomarker (Thome et al., 2017) for assessing the integrity of the interactivity of the cerebral and cardiovascular systems and autonomic regulation of the myocardium, respectively (Appelhans and Luecken, 2006; Thayer and Lane, 2009). Because of the wide field of applications and the importance of cardiovascular autonomic control in healthy individuals during stress, well-being (Grippo, 2017) and various diseases (Appelhans and Luecken, 2006; Ernst, 2017; Montano et al., 2009; Stein et al., 2000), HRV can be metaphorically denoted as the "window into autonomic tone-control" (Friedman and Thayer, 1998).

The goal of this paper is to illustrate the foundations of HRV, describe its characteristics in some salient clinical conditions, its implications for emotion and emotion regulation and to offer an outlook on how spontaneous and controlled breathing impacts organismic oscillations and how findings could be used to improve psychological and physical function. Finally, we introduce some novel results on low frequency (LF)-HRV oscillations in healthy individuals during participation in a first ever MRI scan associated with increased anxiety. Specifically, we suggest to split the LF-HRV into two distinct bands (above and below 0.1 Hz) with the lower band (0.06–0.1 Hz) being sensitive to vascular mechanisms of sympathetic origin and the upper band (0.1–0.15 Hz) probably indexing central commands via vagal efference.

1.1. HRV and its origin

The sinoatrial node (SA-node) as the primary intrinsic pacemaker of the heart initiates each cardiac cycle through spontaneous depolarization of its autorhythmic fibers with an intrinsic firing rate of about 100 beats per minute (BPM) in middle aged humans (Opthof, 2000). The SA-node is regulated by *sympathetic* and *parasympathetic* neurons of the autonomic nervous system. While sympathetic activity induces positive chronotropic effects on a scale of seconds, parasympathetic activity induces negative and parasympathetic withdrawal induces positive chronotropic effects on a scale of milliseconds (Warner and Cox, 1962). The average heart rate in middle aged adults of about 60–80 BPM at rest and 70–90 BPM during low to moderate activities of daily living (walking, being at the office) demonstrate the vagal dominance of heart rate control through inhibition and disinhibition of the intrinsic heart rate. In contrast to the classical assumptions that parasympathetic and sympathetic branches of the autonomic nervous system are influencing each other in reciprocal ways (Pagani et al., 1997), there are also circumstances in both health and disease in which sympathetic and parasympathetic efferences act in a synergistic manner (Paton et al., 2005). Correspondingly, in their seminal review, Berntson et al. (1991) have questioned that a single vector from parasympathetic to sympathetic dominance accounts for the complexities of autonomic control observed in diverse psychophysiological studies. They demonstrated that a two-dimensional autonomic space allowing coupled and uncoupled reciprocal as well as non-reciprocal modes (i.e., coactivation and coinhibition) of sympathetic and parasympathetic efferences is more adequate in modeling autonomic outcomes. Inputs from baroreceptors, chemoreceptors, proprioreceptors and nasopharyngeal receptors are integrated in the central reflex control of autonomic outflow and constitute examples of coupled and uncoupled reciprocal activation. The sympathetic and parasympathetic cardiac branches have been described to act in a coupled reciprocal manner in response to baroreceptor stimulation, whereas in response to stimulation of chemoreceptor and nasopharyngeal inputs, both cardiac sympathetic and parasympathetic innervation is increased, suggesting non-reciprocal coactivation (Silvani et al., 2016). The neural control of the heart varies as a function of effector tissue such that the sympathetic and parasympathetic influences may show nonlinear and non-additive effects. The most well-known of these interactions is termed accentuated antagonism and is associated with parasympathetic dominance over sympathetic influences (Levy and Zieske, 1969; Uijtdehaage and Thayer, 2000).

The central autonomic network (CAN) affects the autonomic neural activity and remotely regulates oscillations of heart rate (Benarroch, 1993). This network is an integrated component of an internal regulation system through which visceromotor, neuroendocrine, and behavioral responses are controlled by the brain. The CAN includes the anterior cingulate, insular, orbitofrontal, and ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus, the periaquaductal grey matter, the parabrachial nucleus, the nucleus of the solitary tract, the nucleus ambiguus, the ventrolateral medulla, the ventromedial medulla, and the medullary tegmental field. These components are reciprocally interconnected, thus allowing bidirectional communication between lower and higher levels of the central nervous system (reviewed by Silvani et al., 2016; Smith et al., 2017; Thayer and Lane, 2009). The output of the CAN is linked to HRV by the interaction of both complementary neuro-vegetative components with inputs to the heart producing the complex variability of the time series of sequential

heart beats (Appelhans and Luecken, 2006; Benarroch, 1993; Saul et al., 1988). HRV can thus be considered as a measure of neurocardiac function that reflects interactions between heart, brain and autonomic nervous system dynamics (Shaffer et al., 2014).

HRV measures may vary between two extremes. Under clinical intensive care settings HRV can be very low approaching values close to zero in pathologic complete cessation of the brain to heart control (Schwarz, 1990; Schwarz et al., 1987) and after surgical interruption of the heart to brain communication (Schwarz et al., 1994). These results support the assumption that heart and brain are connected bidirectionally via neuro-vegetative pathways (Thayer et al., 2012). On the contrary, under experimental (Vaschillo et al., 2006) as well as clinical conditions (Lehrer, 2013) maximal increases in the amplitude of heart rate oscillations are triggered when the cardiovascular system is rhythmically stimulated by paced forced breathing at a frequency of about 0.1 Hz (~6 breaths per minute). These findings suggest that interacting bioelectrical mechanisms of the heart-brain axis generating and modulating HRV are functioning not only as diagnostic *reflectors*, but also as functional *effectors* in the context of neuro-vegetative control, because the mechanisms involved can impact the brain and subsequently even emotional function (Lehrer and Gevirtz, 2014; Mather and Thayer, 2018; Patron et al., 2019). The 0.1 Hz frequency is denoted as the "resonance frequency" at which paced breathing induces high amplitude oscillations in heart rate (Lehrer, 2013). Breathing at this frequency stimulates and strengthens the baroreflex system (Lehrer et al., 2003) and has been shown to be primarily vagally mediated (Kromenacker et al., 2018). Projections to other systems could enhance regulatory brain networks by entraining brain rhythms, and various beneficial effects of HRV biofeedback have been reported (Lehrer, 2013; Mather and Thayer, 2018).

1.2. HRV measurement in the time and frequency domain, and non-linear dynamics of HRV

Providing a comprehensive overview of HRV metrics is beyond the scope of this article. There are, however, several recent scholary reviews on the fundamentals of HRV (e.g., de Geus et al., 2019; Laborde et al., 2017; Shaffer and Ginsberg, 2017; Shaffer et al., 2014), which the reader may consult. A number of techniques have been developed to quantify the beat-to-beat variability in order to evaluate cardiac autonomic regulation in both health and disease. There are two primary approaches for the analysis of HRV, the time domain and frequency domain methods (Shaffer and Ginsberg, 2017; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Other methods based on nonlinear techniques have also been utilized, but less often reported (Laborde et al., 2017). The *time domain* methods utilize either statistical or geometric approaches and rely on a continuous electrocardiographic (ECG) record, which allows the calculation either of heart rate at any point in time or the intervals between successive normal beats. Descriptive time domain variables are the mean normal-to-normal (NN) interval, mean heart rate, and the range for a given time interval. In addition, the Standard Deviation of the NN interval (SDNN) is one of the most widely used time domain indices of HRV and quantifies the total variability that arises from both periodic and random sources. The Root Mean Sum of Squared Successive Differences (RMSSD) and the proportion of NN differences exceeding 50 milliseconds rank among the most commonly used time domain measures of short-term variation and signify high frequency variations in heart rate of mainly parasympathetic (i.e., vagal) origin. These measures are highly correlated and have been found, among others, to signal risk for coronary lesions in stable angina pectoris (Feng et al., 2015). SDNN, SDNN index and RMSSD have proven useful in clinical research (Malliani et al., 1994) as shown, for example, for diabetic neuropathia (Murray et al., 1975) and acute myocardial infarction (Kleiger et al., 1987). The HRV(%) is the normalized SDNN [HRV(%) = SD * T^{-1} × 100; T = average RR-interval] and thus accounts for mean heart period. It is sometimes used for monitoring in intensive care units (Litscher et al., 1993; Schwarz et al., 1987). For a recent discussion of the confounding of heart period in HRV indices please refer to de Geus et al. (2019).

Frequency domain methods partition the total variance of a continuous series of beats into frequency components. Power spectral density analysis provides the basic information of how power distributes as a function of frequency (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In this way, oscillatory components hidden in the variability signal can be detected. For relatively short-term HRV three main frequency bands can be distinguished; (a) the high frequency (HF) band (0.15–0.40 Hz), which reflects effects of respiration on heart rate, also referred to as respiratory sinus arrhythmia (RSA) and mirrors the degree of vagally mediated heart rate variability (vmHRV); (b) the low frequency (LF) band (0.04–0.15 Hz), which represents oscillations related to regulation of blood pressure and vasomotor tone (the so called Mayer-waves) including the 0.1 Hz oscillations; and (c) the very low frequency (VLF) band (<0.04 Hz), which is thought to relate, among other factors, to thermoregulation, kidney functioning and metabolic processes. The various measures of HRV have been summarized previously in detail (e.g., Laborde et al., 2017; Shaffer and Ginsberg, 2017; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Non-linear dynamics and fractal measures of HRV account for the non-deterministic nature of individual heart beats. A variety of different quantifications have been suggested, like detrended fluctuation analysis (DFA), the Poincaré plot with the dimensions SD1 and SD2, sample entropy, Lyapunov exponent, or fractal measures (Costa et al., 2017; Goldberger, 1991; Voss et al., 2009; Yaniv et al., 2013). Contrary to time domain or frequency domain measures of HRV, non-linear dynamic measures account for the non-stationarity, non-linearity and non-equilibrium of the signal, thus describing its complexity. For example, fragmentation analysis of heart rate dynamics quantifies the signal's irregularity, via analyzing the overall pattern of heart rate accelerations and decelerations (e.g., Costa et al., 2017). The general idea behind such measures is that a higher complexity of the heart rate time series signals flexibility and better health (Penttilä et al., 2003), but some forms of unpredictability (e.g., fragmentation) may index non-vagal sources of pathological value. It should be noted though that non-linear dynamic measures of HRV have been studied less extensively than time and frequency-domain measures in previous research and the potential benefits of such measures is under debate (e.g., Glass, 2009; Sassi et al., 2015). Therefore, this review will mainly focus on time and frequency domain measures of HRV.

2. Special issues of critical care medicine, clinical contexts and HRV

2.1. HRV in brain death

In brain dead individuals, the circulatory support includes usually volume substitution, hormonal replacement and inotrope/vascular pressor agents. The duration of the status of brain death is variable depending on several preconditions (e.g. type and location of brain lesion, confounders of various etiology) as well as measures for diagnostic procedures and is regulated by the national brain death codes. From the view of transplant medicine 12–15 h

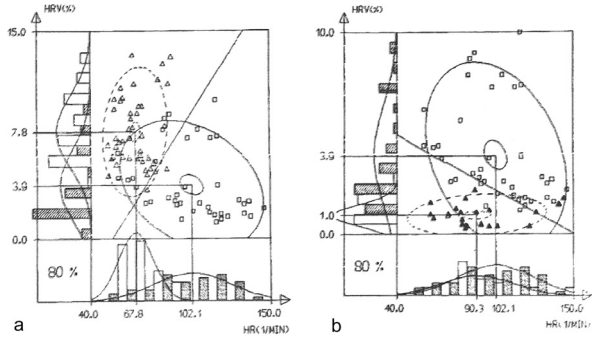

Fig. 1. (a) Bivariate distributions of heart rate (HR; x-axis) and HRV (y-axis) for normal participants (Δ) and comatose patients excluding brain dead subjects (□). The graph shows the 80% confidence ellipses, the discrimination line, the actual (bars) and theoretical (normal distribution curves) of the individuals measured. (b) Bivariate distributions of HR (x-axis) and HRV (y-axis) for patients in coma (□) and brain dead patients (▲). The graph shows the 80% confidence ellipses, the discrimination line, the actual (bars) and theoretical (normal distribution curves) of the individuals measured (modified from Schwarz et al., 1987).

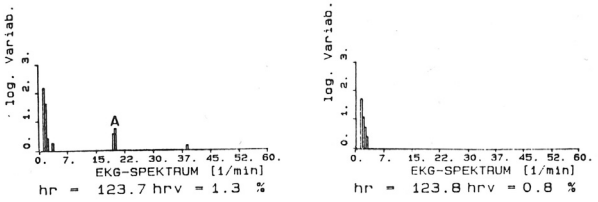

Fig. 2. Heart rate variability (hrv) power spectrum in a control person and brain dead individual. Note the marked reduction/loss of activity in all frequency bands in brain death. The maximal peak in the respiratory band (A) is abolished during diagnostic apnoea testing. (EKG = electrocardiogram, hr = heart rate, log. variab. = logarithmic variability (modified from Schwarz, 1990).

may be the most appropriate time window for allograft function/-survival (Chamorro-Jambrina et al., 2017). In a pioneering methodological and clinical study on brain death and HRV published in 1978, time series analyses of interbeat-intervals were applied to a group of brain dead pediatric patients as well as normal infants and school children, revealing a markedly reduced overall HRV in the patients in comparison to controls (Kero et al., 1978). The authors concluded inter alia that the modulation of heart rate was greatly altered, because of destruction of the vagal nucleus or blockage of vagal efferent pathways. At the beginning of HRV-monitoring under intensive care unit (ICU)-settings in adults with severe brain injuries, this variable gave further insights into the consequences of suppressed/abolished neuro-vegetative control from the brain to the heart and vice versa. In a retrospective comparative study (Schwarz et al., 1987) HRV was derived from severe brain injured intensive care patients (comatose patients with a Glasgow Coma Scale 3–6, brain dead individuals) and healthy controls by calculating average values of HRV and standard deviation presented in percent. The average values of HRV in the group of comatose patients were significantly lower relative to the control group (Fig. 1a), and values were significantly lower in brain death as compared to the group of comatose patients (Fig. 1b). Additionally, in the brain dead group a cutoff value of 2.3% was calculated from the average value of HRV plus 2.5 times the standard deviation. In none of the brain dead patients was HRV higher and in none of the healthy individuals was HRV lower than this value. In a minority of the comatose patients HRV(%)-values <2.3 were found, but in no brain dead patient did HRV(%) exceed 2.3. Hence, it was concluded that in a non-responsive comatose state and suspected complete cessation of cerebral functions the diagnosis "brain death" should be critically revised in the case of HRV (%) >2.3.

The minimized residual HRV in brain death was further qualified by HRV spectral analysis. A sharp peak in the frequency band between 0.15–0.5 Hz was found in brain dead patients. This peak occurred at frequencies that varied from patient to patient, reflecting the ventilator frequency tuned according to individual needs. During the specific diagnostic procedure for the determination of apnea for diagnosing brain death by cessation of artificial ventilation with disconnection of three patients from the respirator, the residual peak in the respiratory band was abolished (Schwarz, 1990). The persisting signals in the respiratory band of spectral analysis of HRV were ascribed to the constant rhythmically and physically mediated transmission of intrathoracic pressure during controlled mechanical ventilation leading to changes of the lung and thoracic excursions. This residual component might also be driven by mechanical stretch effects on atrial receptors or on the sinus node via artificial ventilation (Bernardi et al., 1989). A further finding in brain death was the persisting, but marked decrease of HRV in the LF band (Schwarz, 1990). This finding was confirmed by a study on HRV, blood pressure and baroreflex sensitivity prior and after brain death (Conci, 2001). It has been hypothesized that the suppression of LF-HRV probably reflects the opening of the baroreflex loop induced by deactivation of cardiovascular centers in the brain stem. Furthermore, intrinsic vascular contractile mechanisms located in isolated arterial vessels (Johansson et al., 1966) and vasomotor reflex mechanisms modulated by spinal structures (Conci, 2001) could have contributed to the residually suppressed LF oscillations. An example of the altered power spectrum in brain death as compared to a healthy control is depicted in Fig. 2.

The so called, rigidity of variability" in the context of brain death can be interpreted as an indicator of a cerebro-cardiac disengagement" of the cerebral autonomic control of cardiac functionality during the management of patients with severe cerebral injuries who have the potential of progressing to brain death (Schwarz et al., 1987). HRV could therefore be considered as a method for early confirmation of brain death with high sensitivity (Freitas et al., 1996). However, it should be emphasized that while sensitivity seems to be high, HRV may have low specificity, which has been ascribed to the protocol management of severely head-injured patients including the application of central nervous system depressing drugs (Rapenne et al., 2000). In a later study it was demonstrated that HRV analysis in unsedated comatose patients could provide earlier and more accurate information for the detection of brain death (Vakilian et al., 2011). How the phenomenon of "ventilatory autotriggering" (Schwarz et al 2019) in brain dead subjects may affect the respiratory band or the activity in the residual LF frequency band of HRV spectral analysis has not been studied until now and should be a topic of future investigations. Overall, by taking into account specific pharmacological therapy, neurological pathologies or preexisting pathologic confounders of HRV, continuous HRV-monitoring (especially using spectral and coherence analysis of heart rate and blood pressure) may become a supplemental tool for the management of patients with severe cerebral injuries who are at risk for progressing to brain death (Conci, 2001).

2.2. HRV after heart transplantation and in patients with left ventricular assist devices

An impressive clinical example of a complete iatrogenic discontinuance of the complex interactions between heart and brain in critical care patients is the dissection of the peripheral afferent and efferent neuro-vegetative branches in heart transplantation, which is occasionally considered the only effective treatment for patients with severe heart failure unresponsive to other therapeu-

tic aproaches. Using a multiparametric monitoring system, which simultaneously recorded oscillations of heart rate, respiration and blood pressure (Litscher et al., 1993), HRV was analyzed in adult organ recipients in a time span of about 1.5–3.0 years after orthotopic heart transplantation and in a control group of healthy adult volunteers (Schwarz et al., 1994). In comparison to healthy controls, the frequency bands <0.05 Hz and 0.05–0.15 Hz were significantly reduced in patients after heart transplantation. Interestingly, values in the frequency bands 0.15–0.5 Hz and >0.5 Hz did not significantly differ between groups. The time domain analysis of global HRV calculated from the mean values of RR-intervals and standard deviation given in percent (HRV%) in patients after orthotopic heart transplantation revealed a significant suppression in comparison to the control group of healthy volunteers (Fig. 3).

Noteworthy, there seems to be no overall extinction of HRV after heart transplantation. Specifically, suppression of HF-HRV (respiratory band) was not as pronounced in relation to the entire spectrum. It was hypothesized that the mainly functionally preserved and cerebral mediated autonomic control of respiration (with slight rigidity of respiratory oscillations) may have impacted HRV by means of mechanical biophysical mechanisms, such as changes in the cardiac filling volume and the position of the electrical axis of the heart (via spontaneous oscillations of respiration through the variability of excursions of lung, thorax and diaphragm). In this report it was suggested that HRV could be used to index neuro-vegetative re-innervation after heart transplantation (Schwarz et al., 1994). This hypothesis was later confirmed by Ramaekers et al. (1996), who found that the recurrence of HF-HRV is caused by parasympathetic cardiac re-innervation. A HF component of normal amplitude was observed in a minority of cardiac transplant recipients (6%), but the evolution over time of this component was considered compatible with a gradual parasympathetic re-innervation of the sinus node, thus suggesting that HRV could be a marker for parasympathetic re-innervation (Ramaekers et al., 1996). Nonetheless, the potential role of the activity of intrinsic cardiac neurons (Armour, 1991) in this respect remains largely unknown.

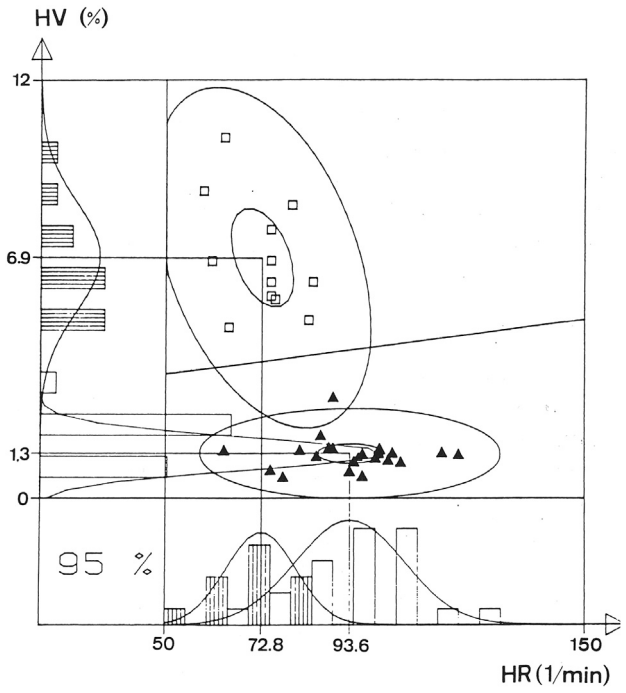

Fig. 3. Bivariate distributions of heart rate (HR; x-axis) and HRV (y-axis) for normals (□) and patients after heart transplantation (▲). The graph shows the 95% confidence ellipses, the discrimination line, the actual (bars) and theoretical (normal distribution curves) of the individuals measured (modified from Schwarz et al., 1994).

The implantation of a left ventricular assist device (LVAD) has become a life-sustaining approach in hemodynamic deterioration with intractable heart failure (McCarthy, 1995). This technique applies to emergency cases as a bridge-to-transplant, or for patients who do not meet the transplantation prerequisites and the number of applications of LAVDs is worldwide higher than that of cardiac transplantations (Hanke et al., 2015). In order to ensure a stable level of blood pressure, the cardiac output of a LAVD supported heart is closely regulated by the programming mode. Although the autonomic nervous system still innervates the native heart, the left ventricle hardly contributes to the cardiac output. Thus, oscillations in blood pressure are driven primarily by the output programming of the LVAD. Therefore, blood pressure oscillations seem to be dissociated from RR-interval oscillations in these patients (Cooley et al., 1998). The characteristic reduction or absence of LF-HRV signaling an autonomic imbalance in severe heart failure (van de Borne et al., 1997) can be restored by circulatory support with the LVAD (Gardiwal et al., 2010). Of note, newly restored predominant LF oscillations (regardless of any effects of blood pressure regulation by comprehensible oscillatory baroreflex input) seem to support the hypothesis of the existence of a central pacemaker for the generation of LF autonomic oscillations (Cooley et al., 1998).

2.3. HRV and weaning from respirator support

An international utilization review (prevalence study) including 412 intensive care units of four North American and European countries reports an average of 39% of patients who received mechanical ventilation, but there are variations in the preference caused by differences in type of ICU, admission and discharge policies, and patient profiles (Esteban et al., 2000). Weaning patients with respiratory insufficiency from ventilatory support represents the period of transition from mechanical ventilation to spontaneous breathing and is one of the most challenging aspects in intensive care involving complex interactions between cardiopulmonary reserve, autonomic function, and musculoskeletal capacity (Vassilakopoulos et al., 1996). When the cause of acute respiratory failure has been resolved, mechanical ventilation should be terminated. However, 20% to 30% of patients experience difficulties in the transition to spontaneous breathing (Heunks and van der Hoeven, 2010). The weaning failure is defined as the failure to pass a spontaneous-breathing trial or the need for reintubation within 48 hours following extubation (Boles et al., 2007). Besides dysfunctions of several organic functional systems, anxiety, depression and delirium are considered the main psychological disturbances that may interfere with successful weaning (Rothenhausler et al., 2000). A prospective observational study demonstrated that in failed spontaneous breathing after disconnection from respirator support, HRV was reduced. The overall diminished HRV may be considered as an independent predictor of weaning results from mechanical ventilation (Huang et al., 2014). Of note, other than the total power of HRV, the change of VLF (<0.04 Hz) was useful in risk stratification for predicting extubation outcome. However, methodological issues (e.g., the definition of a criterion for failed spontaneous breathing in often tachypneic patients during the weaning phase with respiratory rates outside the range of 0.15–0.4 Hz to compute HF-HRV) should be critically taken into consideration (van de Louw, 2014).

2.4. HRV and brain maturation in preterm infants

Preterm birth is commonly defined as any birth before 37 weeks of gestation and occurs about 7–12% of the time (Martin et al.,

2008; Weichert et al., 2015), but the rates vary geographically and within ethnic origins (Shapiro-Mendoza and Lackritz, 2012). In order to reduce the risk of morbidity and mortality, premature infants usually receive care in a neonatal ICU with special control and supplementation of thermal balance, ventilation/oxygenation, hemodynamics, nutrition, and prevention of infections (Lawn et al., 2013). In line with the observation of the recurrence of HRV following orthotopic heart transplantation (Ramaekers et al., 1996), the hypothesis was proposed that HRV could also be a marker of biogenetic growth of the autonomic brain-to-heart feedback control system in newborns. According to the assumption of a dynamic biological development of neural connectivity a common analysis of electroencephalogram (EEG) and HRV was performed to monitor the evolution of cerebral and autonomic functioning during the maturational processes in infants after preterm birth (Pfurtscheller et al., 2008). Of note, there is evidence that during maturation both heart rate and temporal patterns in the EEG are highly variable. At a conceptional age of approximately 36 weeks the nocturnal EEG during quiet sleep shows a semi-discontinuous pattern (Clancy, 1998) accompanied by a low HRV (Rosenstock et al., 1999). In a study aimed to confirm the coupling between heart rate and brain via correlating EEG burst-to-burst intervals (intervals between slow waves of higher voltage activity of short duration interposed into low-voltage activity) with heart rate changes during maturation in preterm infants, data were recorded from a group of neurologically healthy premature infants with a gestational age of about 32 weeks corresponding to a conceptional age of 36 weeks at the time of examination (Pfurtscheller et al., 2008). HRV was calculated in the time domain from the instantaneous heart rate in a selected time window. In order to analyze the EEG burst-to-burst intervals the cumulative density function of the spontaneous variance was calculated and a threshold (defined as the 30% percentile) was used for EEG burst detection. The authors detected a decrease of EEG burst-to-burst intervals accompanied by an elevated heart rate and a significant increase of HRV during maturation in healthy preterm infants. The positive correlation between conceptional age within the observation period of about two weeks and HRV is graphically presented in Fig. 4.

In addition to the findings of changes of HRV in the reinnervation after heart transplantation, the results from the study

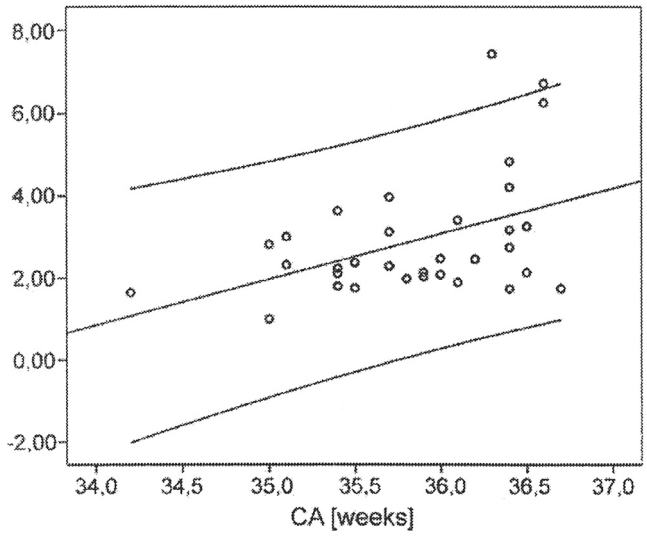

Fig. 4. Scatter plot depicting the correlation between conceptional age (CA) and heart rate variability (HRV[%]). The best-fit linear regression line and a 95% confidence interval are also plotted in the diagram (modified from Pfurtscheller et al., 2008).

during maturation of the brain in preterm infants nicely illustrates that HRV allows the detection of the fine-grained dynamics in fine-tuning of transformation and generation of new connective processes within the neuro-vegetative self-regulatory system. Together, the examples of various severe functional impairments in intensive care patients indicate that a significant suppression of the variability of beat-to-beat intervals of the heart reflects a so-called "decomplexification" (Goldstein et al., 1998) of the human physiology, because connections among cells, organs and tissues are uncoupled and this is proportional to the severity of the critical illness. However, the potential recovery of HRV parameters seems to be associated with clinical improvement and survival (Goldstein et al., 1998). Therefore, the analysis of HRV holds promise as a noninvasive supplementary tool in the evaluation of homeostasis in selected areas of high end" medicine.

2.5. HRV and inflammation

The autonomic nervous system is involved in the regulation of innate immune responses and inflammation through neuroendocrine mechanisms (Elenkov et al., 2000; Maier et al., 1998) and is described as a centrally integrated neural reflex (Pavlov and Tracey, 2012). The cholinergic anti-inflammatory reflex is based on an afferent vagal signaling pathway activated by pathogens or cytokines as well as an efferent vagally mediated pathway that regulates inflammation and pro-inflammatory cytokine release from acetylcholine-synthesizing T-cells such as interleukin 6 (IL-6). Accordingly, plasma levels of pro-inflammatory cytokines increase in cervical or subdiaphragmatic vagotomy, while vagal stimulation or acetylcholine decrease these cytokines (Zila et al., 2017). A recent meta analysis on various measures of HRV and multiple indicators of inflammation from 51 studies (Williams et al., 2019) showed a negative correlation between HF-HRV and IL-6 with $r = -0.13$ (n = 3249, k = 15, $p < .001$) and HF-HRV and C-reactive protein (CRP) with $r = -0.11$ (n = 12,531, k = 25, $p < .001$). The authors concluded that measures of HRV can be used to index activity of the neurophysiological pathway responsible for adaptive regulation of inflammatory processes in humans. A longitudional study in employees showed lower vagally mediated HRV at baseline to be associated with increased high sensitive CRP 4 years later (Jarczok et al., 2014). A similar but cross sectional association between CRP and vagal measures is found in the open access data from the "Midlife Development in the U.S." study (MIDUS 2, P4; ICPSR No. 4652; N = 847 45%males). Analysing the associations between log-transformed RMSSD or HF-power with log-transformed CRP or IL-6 using Pearson correlation shows an association strength of −0.12 to −0.14. Fig. 5 depicts the association between HF-HRV and CRP.

Of note, this neural reflex has much shorter response times compared to humoral anti-inflammatory pathways such as cortisol release via the hypothalamic–pituitary–adrenal axis (Borovikova et al., 2000). In addition, the release of IL-6 and other cytokines trigger the hepatic synthesis of CRP (Casas et al., 2008) - a well known and potent risk factor for morbidity and mortality from a host of diseases including cardiovascular disease, coronary heart diseases, fibrosis, rheumatoid arthritis, and cancer (Haensel et al., 2008). It has been hypothsized that tumor progression might be slowed down due to the inflammatory control. A recent systematic review and meta analysis on the prediction of survival based on HRV measures in cancer patients (Zhou et al., 2016) carfully concluded that patients with higher vagal nerve activity may predict longer survival (Hazard Ratio 0.70 95% CI [0.60, 0.82]; p < 0.001, I2 = 27%).

A recent study examined the association of a RMSSD to CRP ratio at cancer diagnosis as a prognostic marker of survival in more than 270 fatal cancer patients from two populations (Gidron et al.,

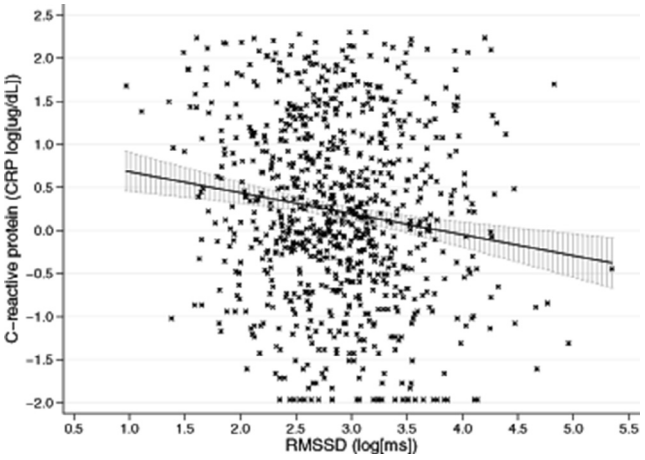

Fig. 5. Scatter plot of vagally-mediated HRV (RMSSD) with the inflammatory measure C-reactive protein from the "Midlife Development in the U.S." study (MIDUS 2, P4; ICPSR No. 4652; N = 847). The regression line is shown (solid line) with the according 95% confidence intervals (grey lines). Data are log-transformed.

2018). The authors report longer survival times (on average +190 days) in cancer patients with a higher RMSSD/CRP ratio. Also, the authors identify a potential clinical utility by therapeutically targeting the RMSSD/CRP ratio, for example, by electrical vagus nerve stimulation in cancer patients, but further studies are needed to evaluate the potential clinical utility of this index. In addition, a translation of this marker to general population samples (vs. patients) may need a more sophisticated approach than a median split of the ratio and may need to include a more proximate (in terms of anti-inflammatory reflex) markers such as IL-6 to be sensitive enough to be of clinical utility.

2.6. Psychological implications

In the previous chapter we outlined findings on HRV signaling brain-heart interactions in individuals with severe clinical conditions and briefly discussed interactions with the immune system with special relevance for tumor progression. It is important to note that severe clinical conditions are often accompanied by emotional disturbances, which are also associated with HRV alterations. In particular, the prevalence of ICU-associated mental health challenges (anxiety, depression, nightmares, sleep disturbances, avoidance) requiring treatment in the post-acute phase is substantial. Anxiety disorders occur in 12–43% of former ICU patients (Eddleston et al., 2000; Scragg et al., 2001), and levels of depression range from 10 to 30% (Davydow et al., 2009; Eddleston et al., 2000; Scragg et al., 2001). Moreover, posttraumatic stress disorder is quite common (up to 64%) among those who survive ICU (Davydow et al., 2009; Griffiths et al., 2007; Rattray and Hull, 2008). Because there is evidence that negative emotions are associated with pathophysiological function, which may interfere with patients' recovery (Moser and Dracup, 1996; Tavazzi et al., 1986), the detection and reduction of emotional burden in critically ill patients are therefore important clinical goals for patient care (McKinley et al., 2004). In the medical environment the spectrum of emotional challenges can be manifold in the context of therapeutic as well as diagnostic measures. Since critically ill patients are often nonverbal and unable to articulate experienced psychological distress, the use of currently available self-report instruments appears inappropriate. Moreover, human emotions vary greatly among individuals and being qualitative phenomena, measuring them with any degree of accuracy is quite challenging (Choi et al., 2017). Hence, the assessment of rhythmic cardiac activity changes potentially signaling higher cognitive functions could prove useful and consequently, several authors suggested that especially vagally-mediated HRV could be an objective tool to assess emotion and emotion regulation (Balzarotti et al., 2017; Beauchaine and Thayer, 2015; Dishman et al., 2000; Williams et al., 2015). In the next chapter we will therefore turn to the presumed close connection between negative emotions and their regulation and HRV.

3. HRV, negative emotions and emotion regulation

Findings based on various methods and study designs strengthen the evidence for a neurovisceral integration model (Thayer and Lane, 2000), suggesting that autonomic regulation and emotion regulation share neural networks within the brain, thus relating emotion regulation and resting HRV with health-related outcomes including morbidity and mortality (Williams et al., 2015). This model originally proposed to account for observed relationships between peripheral physiology, cognitive performance and both mental and physical health and was recently updated and expanded by an eight-level concept of nervous system structures opening new aspects on the hierarchical basis of neurovisceral integration (Smith et al., 2017). The CAN plays a major role in socio-emotional regulatory processes (Riganello et al., 2012; Thayer et al., 2012). Specifically, the anterior cingulate cortex and its projections to the prefrontal cortex, amygdala, hypothalamus, and brainstem (Critchley et al., 2003) shape autonomic efference in response to emotionally meaningful stimuli. The neural output is routed to the sinoatrial node of the heart via the stellate ganglia and the vagus nerve, ultimately modulating its activity (i.e, change in heart rate). Therefore, the non-invasive measurement of cardiac activity changes (i.e., vagally-mediated HRV) may allow to uncover the neural structures involved in affective and autonomic regulation (Bassett, 2016; Kuo et al., 2005; Thayer and Lane, 2009).

Emotional regulation is an important factor in health and disease. Emotions represent the distillation of an organism's ongoing interactions with the environment and the associated threats and challenges as well as the resources to meet those challenges. Importantly, successful regulation of emotions allows for the organism to produce a context appropriate response and thus minimize the wear and tear on the system. We and others have previously proposed that resting HRV reflecting primary vagal efference (i.e., indicators of short-term HRV) represents a resource that can be deployed by healthy individuals in the service of emotion regulation (Porges, 1997; Thayer and Lane, 2000). Moreover, phasic changes in vagally-mediated HRV may reflect the degree to which the individual is successful or not at regulating their emotions. Importantly, we have proposed that the default response to environmental challenges is the stress response characterized by the fight or flight response and the associated relative sympathetic nervous system activation (Brosschot et al., 2017; Thayer and Lane, 2009). In the following, we will briefly review research in support of these ideas.

Many conditions including depression, psychopathology in general (Beauchaine and Thayer, 2015), as well as poor physiological health may be associated with difficulties in regulating emotions, especially negative emotions. Such emotion regulation difficulties have been found to be associated with low resting HRV of mainly vagal origin. For example, an inverse relationship has been reported such that greater difficulties in regulating emotions as assessed by the Difficulties in Emotion Regulation Scale were associated with decreased vagally-mediated resting HRV (Williams et al., 2015). Consistent with the sex differences in HRV, the association between emotion regulation difficulties and vagally-

mediated HRV was moderated by sex such that women with lower vagally-mediated HRV reported greater difficulties in emotion regulation compared to men with lower vagally-mediated HRV, whereas women with higher vagally-mediated HRV reported slightly lesser difficulties in emotion regulation compared to all men (Williams et al., 2017). These findings highlight the importance of vagally-mediated resting HRV as a resource that is available to aid in emotion regulation. They also highlight the range of individual differences in the association between vagally-mediated HRV and regulation of emotions.

These individual differences in the association between vagally-mediated HRV and emotion regulation have been explored using a variaty of paradigms including the emotion modulated startle (a startle response to a sudden loud noise, which could get either amplified or attenuated by emotional states), and phasic heart rate responses, as well as phasic HRV responses. In one study it was found that startle responses in the presence of positive, negative, and neutral affective foregrounds varied as a function of resting HRV (Ruiz-Padial et al., 2003). Specifically, individuals in the highest quartile of vagally-mediated resting HRV showed the context appropriate startle potentiation in the presence of negative affective foregrounds and attentuation in the presence of positive affective foregrounds relative to neutral foregrounds. Importantly, consistent with the idea of the default stress response, individuals in the lowest quartile of vagally-mediated resting HRV showed potentiated startle responses in the presence of neutral affective foregrounds that did not differ from the startle response to negative affective foregrounds. Those findings have been replicated and extended to affective foregrounds that were presented outside of conscious awareness (Ruiz-Padial and Thayer, 2014). Similar results have been reported using phasic heart rate responses. A recent study in which participants performed a letter identification task in the presence of fearful, disgusting, or neutral background pictures showed that those individuals with higher vagally-mediated resting HRV showed differentiated phasic heart rate responses with larger decelerations to disgust and smaller decelerations to fearful pictures relative to neutral pictures (Ruiz-Padial et al., 2018). Again consistent with the default stress response, those with lower vagally-mediated resting HRV showed undifferentiated phasic heart rate responses to the three picture types that were of the same magnitude as the response to the fearful pictures in the higher HRV group. In addition, a recent neuroimaging study of explicit emotion regulation using reappraisal and response modulation found that higher vagally-mediated HRV during rest was associated with greater amygdala modulation and greater dorsomedial prefrontal cortex activity during regulation of negative emotions via reappraisal (Steinfurth et al., 2018). The authors concluded that persons with lower resting vagally-mediated HRV may have difficulty recruiting prefrontal brain regions in the service of emotion regulation.

Finally, due to the rapid vagal signal transduction between the brain and the heart and vice versa, phasic HRV responses have also been associated with emotional regulation. In an early study, it was reported that alcoholics had lower vagally-mediated resting HRV than matched non-alcoholic participants. Importantly, in response to alcohol cues, those alcoholics with low craving showed a phasic HRV increase and decreased desire to drink whereas those with high craving showed a slight HRV decrease and increased desire to drink (Ingjaldsson et al., 2003). In another study, it was found that successful emotion regulation by either reappraisal or suppression was associated with phasic vagally-mediated increases in HRV (Butler et al., 2006). In a recent ecological momentary assessment study, Schwerdtfeger et al. (2019) found that reappraisal was accompanied by vagally-mediated HRV increases in situations perceived as uncontrollable. It has also been reported that there was a phasic increase in vagally-mediated HRV when wives succesfully regulated their, and their husband's, negative emotions in response to a discussion with their husbands about a topic of concern in their marriage (Smith et al., 2011). More recently it has been reported that in a letter identification task with fearful and neutral background faces, those with high resting vagally-mediated HRV showed a phasic HRV increase to the fearful faces whereas those with low resting HRV showed a phasic HRV decrease (Park et al., 2014). Taken together, these findings suggest that during succesful either implicit or explicit emotion regulation, phasic vagally-mediated HRV increases.

In sum, the studies reviewed here suggest that resting or tonic vagally-mediated HRV is a resource that can be brought to bear when regulating emotions, especially negative ones. Moreover, there are significant individual differences such that those with low resting HRV are more likely to show the default stress response whereas those with higher resting HRV are more likely to show context appropriate emotional responses across a range of response measures.

3.1. HRV and depression

Affective disorders - namely Major Depression (MD) - are among the most prevalent mental disorders worldwide and due to their associated direct and indirect costs of utmost importance for health policy (Kessler and Bromet, 2013). Furthermore, depression is also an important variable of the global burden of disease (Ferrari et al., 2013; Moussavi et al., 2007). Approximately 8.1% of adults in Germany (female 10.2%; male 6.1%) suffer from depressive symptoms assessed with the Patient Health Questionnaire – PHQ-9 (cut-off $\geq$ 10) with a peak of prevalence between the age of 18 and 29. The lifetime prevalence of a diagnosed depression is about 11.6% (female 15.4%; male 7.8%; Busch et al., 2013).

While well-being and health strongly depend on the ability to regulate emotional and affective states, depression is widely seen as the result of difficulties in regulating emotions. In general, compromised emotion regulation abilities have been related to common mental disorders such as anxiety and depression (including self-harm) - the two most prevalent mental disorders in western countries (Ferrari et al., 2013; Kessler et al., 2009; Saß et al., 2015). As a central aspect, the suffering caused by depression is not necessarily restricted to the patient but tends to include those close to the person. Moreover, research from the Framingham Heart Study has shown that both positive and negative affective states can behave similar to infectious diseases, spreading across social networks (Hill et al., 2010). However, distinguishing the mood changes between clinically significant degrees of depression and those occurring 'normally' remains problematic and it is best to consider the symptoms of depression as occurring on a continuum of severity (Lewinsohn and Seeley, 2000).

A primary goal that has been set in 2009 by the Research Domain Criteria initiative (RDoC) from the National Institute of Mental Health is to develop a classification system for mental health disorders, linking dimensions of psychopathology to neurobiological systems (National Institute of Mental Health, 2017), explicitly specifying, among others, alterations in circadian rhythms. Hence, a candidate that might match to these criteria is the central autonomic network (CAN) activity.

When comparing depressed individuals with healthy controls using resting state measures of HRV, a meta analysis reports firstly reduced vagally-mediated HRV measures in depressed individuals and secondly a negative association with depressive symptom severity *between* subjects (Kemp et al., 2010). A 10-year cross-lagged *within* person study reported a lower likelihood to suffer from incident depressive syptomes at follow up in male civil servants (Whitehall II study) with higher baseline measures of HRV and no depression at baseline. This was not found in female civil servants (Jandackova et al., 2016). Correspondingly, sex differences

in the relationship between HRV and depressive symptoms have been repeatedly found with depressed men (relative to controls) showing lower short-term HRV, but depressed women showing no difference or even elevated HRV (compared to controls) (Garcia et al., 2012; Thayer et al., 1998). Comparing depressed men with depressed women, lower HRV measures are apparent in men (Chambers and Allen, 2007; Verkuil et al., 2015) in addition to blunted circadian variation patterns of vagally-mediated HRV measures (Jarczok et al., 2018a). Also, non-clinical (i.e., healthy) populations reveal similar sex differences in a recent meta analysis. Here the authors report increased short-term HRV in women, indicating that women have higher vagal activity despite higher mean heart rate compared to men (Koenig and Thayer, 2016). Moreover, an animal model of behavioral depression in non-human primates reveal higher 24-h HRV measures and pronounced circadian rhythmicity in behavioral depressed females compared to their non-depressed counterparts (Jarczok et al., 2018b).

In major depressive disorder (MDD), disruptions of circadian patterns, i.e. in temperature (Hasler et al., 2010) or mood symptom severity (Wirz-Justice, 2008), are common and even considered as core symptoms (Bechtel, 2015; Li et al., 2013). Risk factors for MDD include exposure to shift work (McClung, 2013), which is also associated with altered circadian variation pattern of vagal activity (Mauss et al., 2013). Several treatment options in MDD address circadian modulation techniques including sleep deprivation, bright light therapy and some antidepressant medications (Edgar and McClung, 2013). Thus, it is assumed that milder forms of mood disorders might also be associated with altered circadian rhythms, similar to findings in animal models (Jarczok et al., 2018b).

3.2. HRV and anxiety

Higher levels of anxiety may alter cognitive function and induce hypervigilance, distraction, reduced ability to concentrate, altered memory, and confusion (Salmon, 1993). In serious illness elevated anxiety and inadequate management of it can result in poorer outcomes because of potential alterations in autonomic tone, cardiopulmonary function, increased oxygen consumption, and immune function (Fehder, 1999; Frazier et al., 2002; Spalding et al., 2000).

It is well established that HRV is lower in individuals with anxiety disorders relative to controls. The reduced HRV in these individuals may reflect a failure of the capacity to inhibit cognitive, affective, behavioral and physiological responses in their intensity and duration (Chalmers et al., 2014; Friedman, 2007; Levine et al., 2016; Thome et al., 2017). Decreased HRV may also be found in anxiety associated with pain (Appelhans and Luecken, 2006), depression (Kemp et al., 2012) or stress (Thayer et al., 2012). The reductions in HRV are with a few exceptions in line with previous theoretical models, like the neurovisceral integration model (Thayer and Lane, 2000) and the polyvagal theory (Porges and Furman, 2011). Comparing 2086 patients with anxiety disorders and 2294 controls, Chalmers et al. (2014) could show in their meta-analysis that anxiety disorders were accompanied by a lower HF-HRV of moderate to medium effect size, thus suggesting compromised vagal efference. Anxiety studies using non-linear methods are sparse to date, thus precluding meaningful meta-analytic evidence. Various anxiety-related disorders (i.e., panic disorder, post-traumatic stress disorder, generalized anxiety disorder, social anxiety, specific phobias, and mixed/grouped anxiety disorders) have been associated with significant reductions in time domain measures and HF-HRV (Chalmers et al., 2014). In contrast, obsessive–compulsive disorder was not associated with significant HRV reductions. Small sample sizes and common confounds including psychiatric and medical co-morbidity, as well as medication use may contribute to the heterogeneity of effects (Chalmers et al., 2014). It seems interesting to note that anxiety disorders might not adversely impact LF, thus possibly highlighting the specificity of effects on the parasympathetic nervous system, which is more sensitively captured by short-term HRV including RMSSD and HF-HRV.

Summarizing the above mentioned evidence for the role for impaired vagal regulation as a risk factor for cardiovascular disease, tumor progression and all cause mortality, the reviewed findings have important implications for health-related outcomes of patients with diverse anxiety disorders (Kemp et al., 2012; Thayer and Sternberg, 2010). Clinicians are therefore advised to consider comprehensive health risk reduction strategies for anxiety patients, particularly in light of specific pharmacological treatment, which may induce consistent reductions in HF-HRV (Agelink et al., 2002; Baker et al., 2003; Michaloudis et al., 1998; Vogel et al., 1996). It should be kept in mind that non-psychotropic treatment alternatives could be particularly effective for anxiety disorders (Bornas et al., 2012).

4. Low frequency (LF)-HRV

Research on self- and emotion regulation, as well as depression and anxiety mainly focused on short-term measures of HRV, thus targeting primarily vagally-mediated cardiac activity. The reason for this is the fast neural traffic between the heart and the brain via the myelinated vagus nerve originating in the ventral vagal complex within a time frame of approximately 200 ms (e.g., Porges, 2007). Hence, HF-HRV may capture rapid adaptation to changing environmental demands. LF oscillations in heart rate, on the other hand, have also been found to be associated with mortality of various causes and thus seems to play a vital role for the survival of an organism (e.g., Carpeggiani et al., 2005; Galinier et al., 2000; May and Arildsen, 2011). Of note, LF-HRV has been discussed to reflect both sympathetic and parasympathetic efferences and hence, calculating the ratio of LF and HF might provide information about the sympatho-vagal balance of an organism at least under certain conditions (e.g., Shaffer and Ginsberg, 2017). However, it should be emphasized that sympathetic influence on LF-HRV has been challenged recently, thus also questioning the utility and meaningfulness of the often reported LF/HF ratio as an index of autonomic balance (e.g., Billman, 2013; Goldstein et al., 2011; Moak et al., 2007; Reyes del Paso et al., 2013). Interestingly, recent theorizing suggests that 0.1 Hz oscillations in HRV might rather reflect activity of the unmylelinated vagus nerve originating in the dorsal lateral vagal complex (e.g., Porges, 2007). Moreover, a very recent pharmacological blockade study supports the notion that these low frequency oscillations may be of primarily vagal origin as low frequency variability across the 4–9 breaths per minute range was abolished by vagal blockade but relatively unaffected by sympathetic blockade (Kromenacker et al., 2018).

Taken together, the functional meaning of LF-HRV is less well understood. As we will outline below, it has been proposed that breathing at 6/min (~0.1 Hz) could facilitate emotional well-being due to the induction of a physiological coherence (Mather and Thayer, 2018). Thus, LF-HRV might be of special relevance for the study of psycho-physiological interaction. In line with this reasoning, Pfurtscheller et al. (2017b) found evidence for temporary phase coupling between blood oxygen level-dependent (BOLD) signals and RR-interval oscillations with dominant frequencies around 0.10 Hz during increased state anxiety. Consequently, the LF band could prove particularly worthwhile for the study of anxiety and anxiety processing.

4.1. MRI-related anxiety and LF-HRV

In order to examine the interaction of the brain and the heart as related to anxiety in more detail, Pfurtscheller and colleagues

(Pfurtscheller et al., 2018b; Pfurtscheller et al., 2018a) recently analyzed phase locking values between different BOLD signals and between and cardiac beat-to-beat interval (RR-interval or RRI) signals HRV in individuals taking part for the first time in their life in a brain imaging scan. Importantly, the number of Magnetic Resonance Imaging (MRI) procedures is rapidly increasing and therefore detailed knowledge about MRI-related anxiety and its impact on resting state activity is becoming ever more important. While claustrophobic events are observed in only 1.2% of individuals (Munn et al., 2015), anxiety of moderate intensity is prevalent in 25–37% of patients during clinical scans (Katz et al., 1994). A first study on MRI-related anxiety, designed to systematically assess fluctuations of state anxiety during scanning (Chapman et al., 2010) revealed a reasonably strong reduction of anxiety during the first resting state scan and an unexpected moderate increase toward the end of scanning about 50 minutes later. Because changes in anxiety are known to be accompanied by regional brain activation (Bishop et al., 2004) probably impacting task effects, research on adaptation to the scanner and the associated anxiety responses seem warranted.

Pfurtscheller et al. (2017a, 2018a) studied MRI-related anxiety in a group of 23 healthy volunteers without any former MRI experience (scanner-naïve). BOLD data, ECG and respiration were collected in addition to state anxiety (AS) in two resting state measurements separated by ~30 min. AS varied between AS = 11 and AS = 29 (possible range of AS scores: 10–40). As a proxy measure of anxiety processing the change in AS from the first to the second resting state was calculated. Notably, anxiety varied across participants and resting states in a broad range including both low and high anxiety scores. Two groups of individuals were separated, one with a comparably large anxiety decrease (*large anxiety change group)* and one with small changes, no change or even an anxiety increase (*small anxiety change group*). The decrease of anxiety in the *large anxiety change group* was highly significant, while a modest anxiety increase in the *small anxiety change* group reached no significance (see Fig. 6 left side).

The BOLD signals were recorded from precentral gyrus and insula in both hemispheres and subjected to a phase-locking analyses in the band 0.07–0.13 Hz. In contrast to the majority of HRV studies, which used the HF-band (e.g., Jarczok et al., 2014; Laborde et al., 2017; Quintana et al., 2012) or time domain measures of short-term HRV (e.g., RMSSD; Gerteis and Schwerdtfeger, 2016; Gidron et al., 2018; Lane et al., 2009; Ottaviani et al., 2013; Schwerdtfeger and Gerteis, 2014) as the most sensitive indicators of vagal efference, Pfurtscheller and colleagues (Rassler et al., 2018; Pfurtscheller et al., 2018b) focused on the LF-HRV.

The standard LF-HRV covers the 0.04 to 0.15-Hz band (see Section 1.2) and includes frequency components above and below 0.1 Hz. The discrimination between these two components seems important however, because spectral analyses of RR-interval and blood pressure found evidence for two distinct spectral components at 0.08 ± 0.01 Hz and 0.12 ± 0.02 Hz, thus suggesting two separate rhythms within the LF-band (Kuusela et al., 2003). In accordance with this evidence, Pfurtscheller and colleagues analyzed two distinct subtypes within the LF-band, one band below 0.1 Hz (LFa: 0.06–0.10 Hz) and the other above 0.1 Hz (LFb: 0.10–0.14 Hz), and related both components to state anxiety during a MRI scanning. Importantly, the lower LFa band or so-called midfrequency component (commonly defined as 0.04–0.10 Hz) seems to reflect primarily baroreceptor-mediated blood pressure regulation via sympathetic nerve fibers (Friedman, 2007) and thus should be more sensitive to sympathetic efference. To the authors' knowledge, the higher LF-component (0.10–0.14 Hz) has not been examined so far. Whether sympathetic and/or vagal influences contribute to this LFb band is yet unknown.

For the combined sample of 23 individuals there was a significant increase in LFa power from the first to the second resting state and no change in LFb power. In contrast, both anxiety groups seemed to exhibit different trajectories for LFa and LFb-components, respectively, as became evident by a marginally significant interaction of component (LFa vs. LFb), time (resting state 1 vs. resting state 2), and group (large vs. small anxiety change).

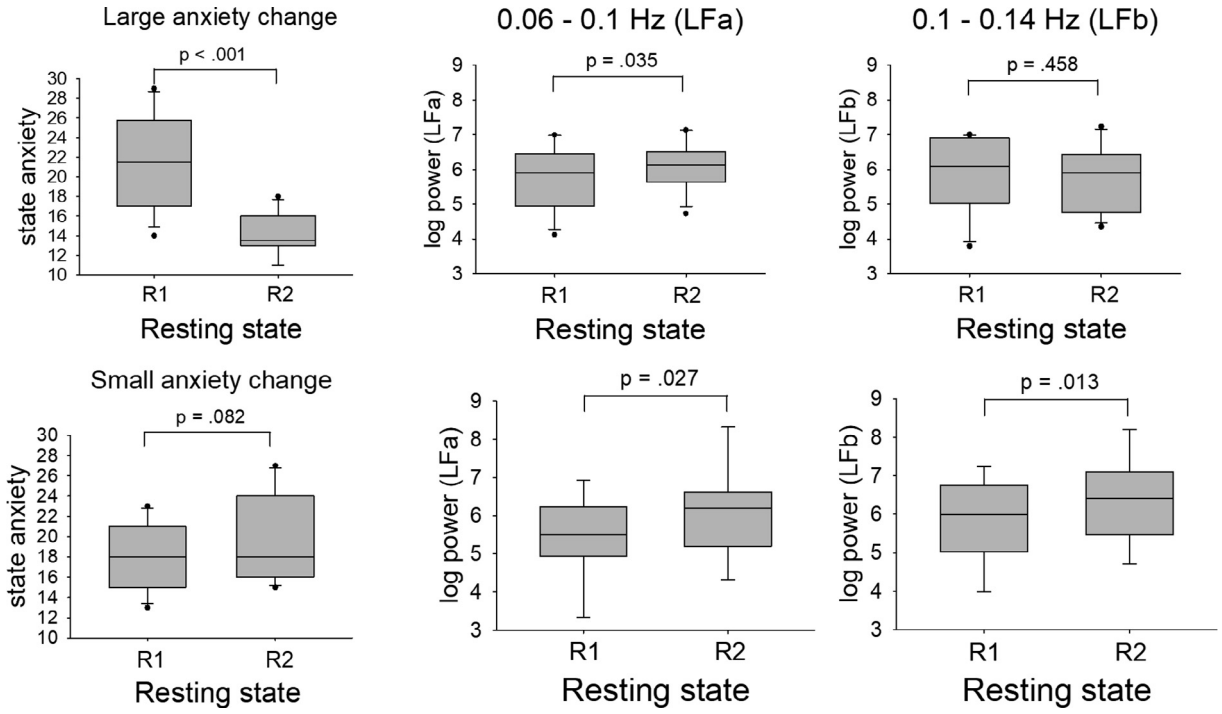

Fig. 6. Boxplots depicting changes of state anxiety, natural log power of LFa and LFb across resting states R1 and R2 for the large anxiety change group (upper panel) and low anxiety change group (lower panel). Note: whiskers indicate the 10th and 90th percentile (modified from Pfurtscheller et al., 2018a).

The results are summarized in the form of boxplots in Fig. 6, separated for each group. It could be proposed that individuals displaying a comparably *large anxiety change* showed an adaptive response to repeated testing, because they exhibited a large decline in anxiety between both resting states. Contrary to that, the *small anxiety change* group seem to not have exhibited regulatory behavior in the course of the session as indicated by either a minor decrease, almost no change or even a modest increase in anxiety between both resting states. It is important to note that within this group anxiety at resting state 1 was lower as compared to the high anxiety change group, thus suggesting that emotion regulation strategies could have been enacted prior to the first scan.

Of note, the *large anxiety change* group showed a divergence of LFa and LFb across time, documenting an increase in LFa and a non-significant change in LFb. Interestingly, the small anxiety change group showed a general increase in both components. It should be mentioned that anxiety has been found to be associated with attenuated HRV of primary vagal origin (e.g., HF-HRV), whereas sympathetic function seems to be elevated (Friedman, 2007).

The findings suggest that the discrimination of two components within the LF band could prove useful for the study of anxiety regulation. Above we speculated about the sympathetic and parasympathetic origin of both LF-components and ascribed a more pronounced sympathetic efference to the lower LFa. A power increase within this component (0.06–0.1 Hz) in the time course as exhibited in both groups might signal large Mayer waves relating blood pressure with heart rate. While the slow oscillations in heart rate index elevated HRV, the enlarged BP oscillations are coupled with an elevated cerebral blood flow velocity (CBFv) in the middle cerebral artery (Diehl et al., 1998) resulting in increased cerebral perfusion. In line with this, Lane et al. (2009) could show that emotion regulation is accompanied by concomitant cerebral blood flow changes in left hemisphere areas in the brain identified as being important for emotion regulation. Hence, the increase in LFa potentially signaling sympathetic efferences could suggest increased cerebral perfusion to provide resources to cope with novel situations. However, the psychological consequences of this neural resource mechanism seem to be different between groups.

It is interesting to note that the LFb-component remained rather unchanged in individuals exhibiting a rather strong decline in anxiety, but increased in individuals with slightly increasing, but intermediate anxiety scores. Further analyses suggested that among individuals showing a comparably strong increase in anxiety between resting states (six participants) power in the frequency range of 0.1–0.14 Hz increased particularly strongly. It seems reasonable to assume that with increasing anxiety the intensity of central commands increases with the goal to manage the uncomfortable situation in the scanner. Therefore, it could be assumed that central commands are reflected in the LFb-component, thus suggesting probably less adaptive emotion regulation strategies to cope with challenging situations, like worry or rumination (e.g., Ottaviani et al., 2016). The rather unexpected unaltered LFb-component in individuals with a strong decline in anxiety certainly warrants further research, but could signal less allocation of effort-related cognitive resources (less mental effort; Mulder and Mulder, 1987), because of distraction, diversion of attention etc. As a final remark it should be noted that mechanisms associated with both LFa power and LFb power increases might operate simultaneously. The prevalence of two frequency components in the LF-band is best documented by the HRV power spectrum with peaks below and above 0.1 Hz. One peak reflects LFa power and presumably cerebral blood flow and the other peak LFb power and may characterize central commands. That is, elevated cerebral perfusion could facilitate diverse cognitive operations. Support for this assumption came from time-varying spectra displaying at the same moment of time spectral power peaks above (LFb) and below 0.1 Hz (LFa) in some participants.

To conclude, based on these findings researchers are advised that MRI-related anxiety might not only be accompanied by enhanced Mayer waves in blood pressure and heart rate, but could also be accompanied by emerging central commands altering cortical excitability fluctuations, thus impacting regional brain activation during resting state measurements (for a further discussion of this topic, see Pfurtscheller et al., 2017b, 2018a).

4.2. Resonance-breathing at 6 breaths/min and emotional well-being

Breathing is the only fundamental rhythm that can be controlled consciously (thinking about each breath) and unconsciously or automatically. It is regulated either by respiratory neurons in the medulla oblongata and pons (metabolic breathing) or influenced from higher centres in the cerebral cortex (so-called behavioral breathing) (Homma and Masaoka, 2008).

A special type of respiration is slow breathing at 6/min (0.1 Hz). Breathing at 0.1 Hz has also been labeled coherent or resonance breathing, because it is suggested to induce a coherent, synchronous resonance frequency in various physiological signals (e.g., HR, baroreceptor reflex, blood pressure, brain perfusion), thus entraining different physiological oscillatory systems (e.g., McCraty et al., 2009; Mejia Mejia et al., 2018). Importantly, it has been suggested that the induction of coherence in oscillatory systems fosters metabolic efficiency of the organism (e.g., McCraty et al., 2009), thus contributing to physical and mental health. The underlying mechanisms of the health benefits are not yet fully understood, but resetting of baroreflex sensitivity and stimulation of vagal efference with an increased adaptability of the cardiovascular system and bottom up effects on the central nervous system, optimized oxygenation in different brain regions, optimized gas and fluid exchange, and increased temporal synchronization of bodily cells are among the most prominent candidates (Kromenacker et al., 2018; Lehrer, 2013; Lehrer and Gevirtz, 2014; McCraty et al., 2009; Russo et al., 2017; Zaccaro et al., 2018). Fig. 7 contrasts spontaneous breathing and resonance breathing at 6 breaths/min in one individual.

The goal of resonance breathing is to engender maximal-amplitude heart rate oscillations, thus increasing LF-HRV, which may in turn affect the above mentioned physiological and also psychological functions including the regulation of negative feeling states and emotions like anxiety and pain (Jafari et al., 2017; Lehrer, 2013; Thayer and Lane, 2009), as well as emotional well-being (Mather and Thayer, 2018; McCraty and Zayas, 2014). The mental health-benefits of resonance breathing may be achieved through upregulation of cerebral blood flow via the vascular branch of the baroreflex. Both the vascular branch of the baroreflex loop with a time lag of about 10 s and the breathing rate at 0.1 Hz create a resonance resulting in high-amplitude oscillations in HR (Mather and Thayer, 2018). In a recent review Zaccaro et al. (2018) document that slow breathing (<10/min) resulted in more adaptive psychological function and better psychological wellbeing, higher alpha and lower theta EEG power, and increased activity in prefrontal, motor and parietal cortices as well as in several subcortical brain regions including the pons, thalamus and hypothalamus. However, brain imaging studies are sparse to date and further research on brain activation is certainly warranted.

It should be mentioned that although findings on the health-related consequences of resonance breathing appear promising, several conundrums remain. First, corresponding studies are hampered by comparably small sample sizes and methodological heterogeneity, and the physiological pathways to psychological well-being are not yet fully understood, thus warranting further examination. Second, it has been reported that effects of 0.1 Hz

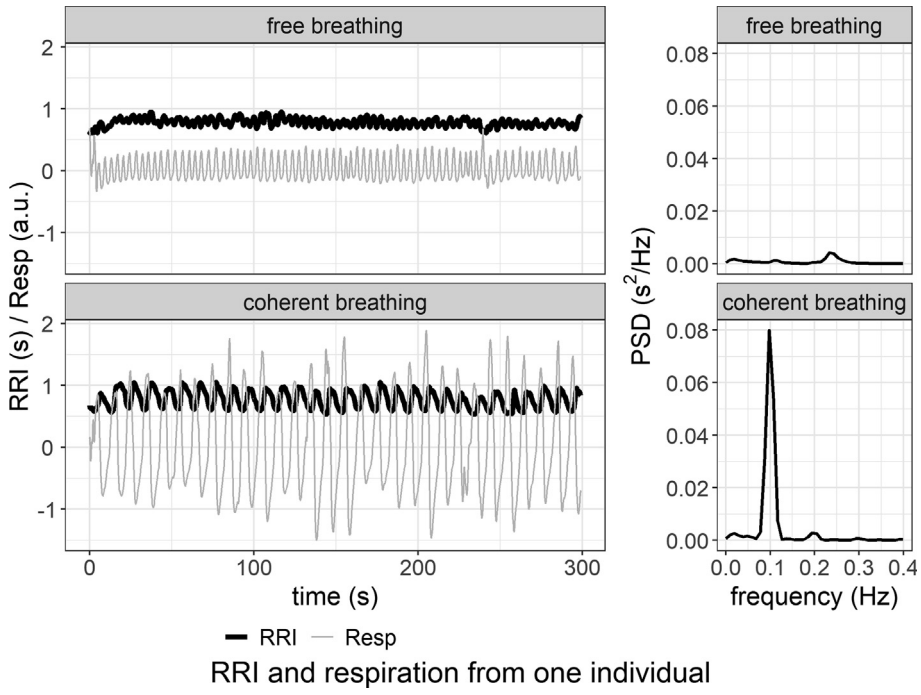

Fig. 7. Example of two recordings from spontaneous breathing (upper panel) to coherent breathing with 6 breaths/min (lower panel) in one individual. The respective power spectra of the RR-intervals (RRI) is depicted on the right side. Fat lines indicate RR-interval and thin lines indicate respiration.

breathing could lead to a slight hyperventilation (Szulczewski and Rynkiewicz, 2018), which might impact psychological outcomes. Hence, effects might depend on the physical fitness or the overall respiratory capacity of an individual. Accordingly, the individual resonance frequency seems to slightly differ between individuals in the range of 0.075–0.12 Hz (e.g., Vaschillo et al., 2006), thus calling for an individualized approach to resonance breathing. Consequently, a protocol has been suggested to adjust the frequency prior to breathing exercises for each individual in order to achieve reliable effects (e.g., Lehrer et al., 2013). Third, the overall pattern of respiration (i.e., same length of inspiration and expiration or longer or shorter expiration than inspiration) needs further research (Szulczewski and Rynkiewicz, 2018). Indeed, studies seldom report the inspiration/expiration ratio, although van Diest et al. (2014) could show that psychological benefits are more likely with a low inspiration/expiration ratio (i.e., longer expiration than inspiration). Fourth, it has been rarely studied to what extend the HR power spectrum changes after breathing exercises and when the presumed stronger vagal efference emerges. Although LF-HRV inevitably increases during 0.1 Hz breathing and this increase may be of vagal origin (Kromenacker et al., 2018), residual power in the HF-range usually remains (van Diest et al., 2014), but the meaningfulness of this pattern is not clear yet. Fifth, studies seldom report whether participants performed nasal or oral breathing. According to Zelano et al. (2016) nasal breathing may synchronize neural activity in the olfactory cortex and limbic brain structures, thus suggesting superior effects on mental health as compared to oral breathing. Finally, it should be noted that regular slow breathing considerably attenuates the complexity of the HRV signal, thus leading to lower non-linear HRV indices (e.g., Penttilä et al., 2003). A more stable, less complex HRV, however, has been associated with poor clinical outcomes, like obstructive sleep apnea and cardiovascular diseases (Jelinek et al., 2013; Melillo et al., 2015; Tobaldini et al., 2013; Trimer et al., 2014; Voss et al., 2009). It should be noted though that HR complexity measures might be distorted when breathing is locked to a specific frequency (i.e., 0.1 Hz) and short-term recordings, which are typical for breathing trials, might not allow an accurate estimation of fractal properties of the HR time series (e.g., Perakakis et al., 2009). Hence, further research is necessary to elucidate the health-related mechanisms of HR complexity as a correlate and consequence of slow breathing exercises.

Despite the above mentioned shortcomings, breathing near resonance frequency appears to promote more adaptive physiological and emotional functioning (with beneficial cardiovascular effects) (Anderson et al., 2010; Steffen et al., 2017) and could therefore constitute a non-pharmacological and non-invasive tool in critically ill patients for stabilization in the acute and recovery phase as well as a preventive strategy to facilitate adaptation. Further studies on this specific patient population are certainly worthwhile.

4.3. Spontaneous slow breathing and cessation of RSA

One fundamental physiological principle is that inspiration is associated with heart rate acceleration (RR-interval decrease) and expiration with a heart rate deceleration (RR-interval increase), which is commonly referred to as respiratory sinus arrhythmia (RSA) (e.g., Rottenberg et al., 2007; Yasuma and Hayano, 2004). RSA quantifies mainly vagally-mediated HRV and is associated with a variety of self-regulatory processes (Grossman and Taylor, 2007; Porges, 1995; Rottenberg et al., 2007). An example for RSA is depicted in Fig. 8 upper panel with RR-interval and respiration signals out-of phase (inspiration associated with RR-interval decrease).

However, RSA might not be considered a universal phenomenon, since there seems to be exceptions documented recently by a re-analysis of the MRI/anxiety data (Pfurtscheller et al., 2019; Rassler et al., 2018). Specifically, it was observed that RSA could be "switched-off" in a minority of participants exhibiting slow breathing waves with alternating dominant frequencies of 0.1 Hz (6 breaths/min) and 0.15 Hz (9 breaths/min) during resting state recording. The maximum of inspiration coincided with the largest RR-interval (maximal bradycardia) and hence was in sharp con-

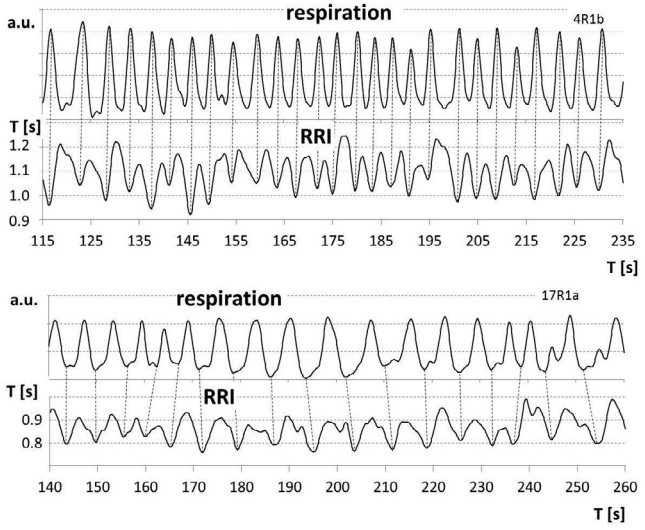

Fig. 8. Example from two participants one with classical RSA (upper panel) and another with cessation of RSA (lower panel; modified from Rassler et al., 2018).

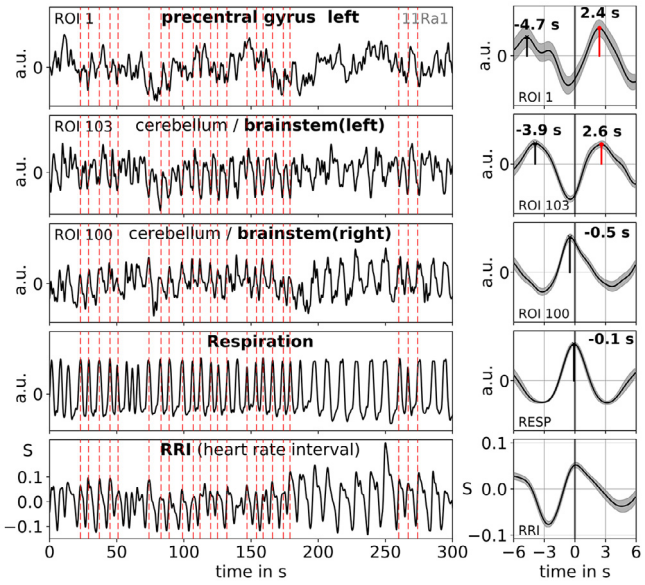

Fig. 9. Ongoing BOLD signals from precentral gyrus (ROI 1) and cerebellum/brain stem (ROIs 103 and 100), RR-interval and respiration signals from one subject with alternating 0.1 Hz and 0.15 Hz oscillations. Left panel: Maxima (peaks) of RRI oscillations are indexed by vertical dashed lines used as trigger for averaging. Right side: Peaks of the averaged waves (±SE) demonstrate the coincidence of RR-interval, breathing and BOLD (ROI 100; respiratory artefact) oscillations. The first two traces (BOLD ROI 1 and ROI 103) characterize neural BOLD oscillations lagging RR-intervals by 2–3 s (modified from Pfurtscheller et al., 2019).

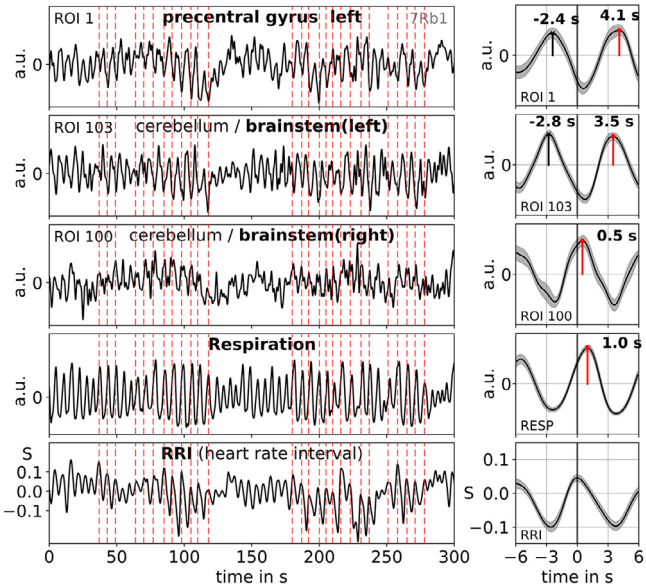

Fig. 10. Examples of ongoing BOLD signals from precentral gyrus (ROI 1) and cerebellum/brain stem (ROIs 103 and 100), RRI and respiration signals for one subject with dominant 0.15-Hz oscillations. For further details see Fig. 9.

trast with RSA signaling RR-interval decrease (heart rate increase) during inspiration and RR-interval increase during expiration. An example is displayed in Fig. 8 (lower panel).

Importantly, beside conscious stimulus-paced resonance breathing typically inducing RSA, the data suggest that there is also evidence for an unconscious, autonomic breathing at 0.1 Hz and/or 0.15 Hz with cessation of RSA. While 0.1-Hz oscillations were observed during 37% ± 10% of 5-min resting state, the 0.15-Hz oscillations were slightly more frequent with 45% ± 15% (Rassler et al., 2018). The occurrence of breathing and RR-interval waves with 7 s duration (0.15 Hz) in some individuals is noteworthy (Rassler et al., 2018), because they resemble the "0.15-Hz rhythm" reported by Perlitz et al. (2004) in the reticular formation of the brain stem (medulla oblongata and pons). This 0.15 Hz rhythm could be characterized by some important features: (a) it is broad-banded ($M \pm SD$: 0.15 ± 0.03 Hz), (b) it is comprised of periods of spindle waves with increasing and decreasing amplitudes, (c) it is phase-synchronized with respiration at 1:1 or 1:2, and (d) it is prevalent not only in neural spindle activity and respiration, but also in heart rate and blood pressure.

Importantly, the 0.1 and 0.15 Hz oscillations outlined above were found not only in respiration and RR-intervals, but also in neural BOLD signals (Pfurtscheller et al., 2018b) and thus could constitute "central pacemaker rhythms for modulating cardiac activity". In detail, two types of BOLD oscillations at 0.1 and/or 0.15 Hz were observed in cerebellum/brain stem, one coupled 1:1 with respiration and RR-interval oscillations, and the other delayed by 2–3 s. The former could be interpreted as respiratory artefact (in-phase with respiration), the other as neural BOLD associated with neural activity changes delayed by the neurovascular coupling time of 2.5 s (Mateo et al., 2017). Two examples of spontaneous BOLD, RR-interval and breathing oscillations during rest, one with a mix of 0.1 Hz and 0.15 Hz oscillations (Fig. 9) and the other with exclusive 0.15-Hz oscillations (Fig. 10) underlines the interaction between brain and cardiovascular-respiratory systems and strongly suggests the existence of a central pacemaker in the brain stem. In order to highlight the coincidence of inspiration and RR-interval increase (i.e., cessation of RSA), some waves (indicated by vertical stippled lines) were averaged time-locked to a few maxima of RR-interval increase.

In this BOLD study not only oscillations in the brain stem were analyzed, but also in the precentral gyrus (first trace in Figs. 9 and 10). Remarkably, the BOLD oscillations in the prefrontal cortex (PFC) coincide nearly perfectly with the BOLD signal (ROI 103) from the brain stem (the averaged BOLD waves match in PFC and brain stem; see right panel of the Figures). This coincidence between PFC and brain stem could be explained in two different ways: First, the pacemaker is located in the brain stem (Perlitz et al., 2004) and through the ascending reticular activation system (ARAS) the PFC is co-activated in parallel to the cardiovascular

nuclei in the brain stem. Second, the pacemaker is in the PFC and activates the cardiovascular nuclei in the brain stem. In order to clarify causal coupling and direction of information flow, respectively, calculations of the Direct Transfer Function based on Granger causality principle could prove particularly worthwhile (Kaminski and Blinowska, 1991).

Perlitz et al. (2004) reported that a 1:2 coupling between spindle activity in the brain stem and respiration could complement a 1:1 coupling. Therefore, a central pacemaker in the brain stem seems likely in individuals with cessation of RSA and 1:2 or 1:3 coupling (i.e., 2 or 3 breaths during one RR-interval cycle). There are first findings in support of this hypothesis using phase coupling (PLV) analysis between BOLD oscillations from the brain stem and RR-interval oscillations in the 0.1–0.15-Hz band. This approach allows to examine pacemaker activity in the brain stem independent of the breathing rate.

To conclude, spontaneous breathing at 6 or 9 breaths/min could therefore constitute an unconsciously applied strategy to increase slow oscillations in uncomfortable or unpleasant contexts with or without claustrophobia, for example, when an individual's head is placed in a scanner, and resources need to be allocated to regulate negative emotions.

5. Conclusions and future prospects

The aim of this review is to demonstrate the clinical implications of oscillations in heart rate (so-called HRV) and to explore the underlying mechanisms. The examples from extreme clinical conditions like brain death and status after heart transplantation confirm the assumption of a close coupling of the brain and the heart in humans. Conditions with a disconnection from central nervous system sources as in heart transplant patients result in a maximal suppression of HRV. Findings on patients with left ventricular assist devices strengthen the hypothesis of centrally generated oscillations of autonomic nervous system outflow. Changes in HRV during re-innervation after heart transplantation and during maturation of the brain in preterm infants give an impression of the high sensitivity of this measure in conjunction with minimal neuro-structural reorganisation/renewal processes and dynamics within the neuro-vegetative self-regulatory system. HRV seems to be also involved in cancer progression as suggested by studies examining the interplay of the autonomic and immune system. Therapeutic implications could be derived either by increasing vagal efference via peripheral electric nerve stimulation or via psychotherapeutic or pharmacological interventions targeting increasing central commands on HRV.

In addition, the evaluation of short-term HRV in the band 0.15–0.4 Hz being particularly sensitive to vagal influence especially in relation with cardiac rhythms could prove fruitful for the study of both depression and anxiety. Moreover, there is cumulating evidence that the regulation of emotions is interlinked with HRV thus potentially offering a valuable tool to assess psychological functioning and mental health in non-verbal, critically ill patients. With respect to recent developments in HRV research on healthy individuals during their first MRI-exposition, it seems important to rethink the limits for differentiation between HF and LF bands at 0.15 Hz. Splitting the LF-HRV in bands above and below 0.1 Hz (0.06–0.10 Hz; 0.10–0.14 Hz) could give new insights into the neurophysiological underpinnings of emotion regulation and anxiety processing and might also inform more sensitively about the complex interplay between parasympathetic and sympathetic efferences signaling heart-brain interctions.

For some participants fMRI scanning is an uncomfortable, even claustrophobic experience, which may provoke pronounced feelings of anxiety (Munn et al., 2015; Pfurtscheller et al., 2018b; Rassler et al., 2018), which could trigger a respiratory pattern with dominant 6–9 breaths/min. Such a slow breathing rate not only elevates HRV, thus constituting a potential resource for anxiety processing, but could also modulate the spontaneous resting state activity. Hence, special attention seems warranted when scanning results are interpreted, because anxiety processing might also induce a hemispheric asymmetry. Spontaneous (unconscious) slow breating at 6–9/min could facilitate processing of negative emotions, while stimulus-paced (conscious) slow breathing at 6/min could reinforce positive emotions, ultimately increasing subjective well-being.

Irrespective of the above mentioned evidence, it should be kept in mind that findings on HRV stemming from somatically healthy individuals cannot necessarily be generalized to critically ill patients due to diverse possible confounders caused by primary cerebral or extracerebral lesions, co-morbidity and treatment (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Relatedly, in agreement with other authors (Mazzeo et al., 2011) it can be concluded that recent developments as outlined here may help in amending diagnostic and therapeutic practice to bear clinical benefits. Future prospective investigations with special focus on the link between anxiety and depression in connection with HRV and the outcome of critically ill patients could help to determine which patient populations should be monitored for HRV analysis. Finally, it should be noted that although partitioning variance into different frequencies allows to draw firm conclusions about the autonomic nervous system functioning and its interaction with higher central information processing, it neglects the complexities of cardiac activity (Goldberger, 1991; Sassi et al., 2015). Heart rate complexity has less often been studied, but seems crucial for an individual's survival. Consequently, future research should focus more strongly on these measures in addition to traditional time and frequency domain quantifications of HRV and to evaluate their clinical usefulness.

Declaration of Competing Interest

The authors declare no conflict of interests.

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