Heart rate variability and slow-paced breathing: when coherence meets resonance

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Highlights

- Slow-paced breathing is at the origin of improved well-being through multiple pathways
- Slow-paced breathing increases blood pressure and cardiac oscillations
- Temporal coherence of respiratory, blood pressure, and cardiac oscillations is achieved only at the resonant frequency (~ 0.1 Hz)
- Coherence of phases at the resonant frequency improves vagally-mediated heart rate variability and baroreflex sensitivity, which may be responsible for the reduction of cardiac events, hypertension, muscle frailty, and inflammation.
- Vagal afferents, stimulated by increased respiratory-induced pressure oscillations, activate directly and indirectly limbic and interoceptive areas, to possibly trigger improvements in awareness, cognition, and stress management.

Abstract

Clinical research on the beneficial effects induced by slow-paced breathing has been increasingly extended in the past twenty years. Improvements in cardiovascular functioning, executive functions, or stress management appear to be among the most prominent observations in these studies. However, the mechanisms underlying these effects are multiple and complex. This review will focus on the importance of reducing breathing rate at the resonant frequency (~ 0.1 Hz), which increases cardiac oscillations, thus reflecting improved vagally-mediated heart rate variability and baroreflex sensitivity. These effects are achieved through temporal coherence of respiratory, blood pressure, and cardiac phases, which are the origin of multiple peripheral benefits. In return, vagal afferents, which send inputs to interoceptive areas, are stimulated for longer and more intensely than when breathing spontaneously. In limbic areas, which may also be stimulated through larger cerebral blood flow oscillations and increases in oxygen delivery, interoceptive activation produces a cascade of neural activations that may be at the origin of the central benefits of deep and slow-paced breathing.

Keywords: deep breathing, thoracic breathing, slow-paced respiration, vagus nerve, parasympathetic nervous system, baroreflex, resonance, cardiac coherence

I- Introduction

Breathing can be considered a specific phenomenon among the different functions of the autonomic nervous system (ANS). Although the respiratory system functions mostly automatically, without requiring the individual's conscious control, it can also be placed under volitional control (Zaccaro et al., 2018). It is historically known that slow-paced breathing (SPB) can help to regulate homeostasis (Russo et al., 2017; Zaccaro et al., 2018). For example, two thousand years ago, the Yoga Sutra of Patanjali suggested that "expiration is linked to mood stability". In the mid-20th century, breathing practices began to spread across the western world when international scientific publications supported the fact that breathing at a low breathing rate had benefits for mental health (Higashi, 1964). As research progressed, Vaschillo, Lehrer, and collaborators described the mechanisms underlying the physiological modifications during SPB realized at 6 cycles per minute (cpm) (Vaschillo et al., 1983; Lehrer et al., 1997; Vaschillo et al., 2002, 2006). The aim of this review is to explore these mechanisms with particular attention to the temporal coherence of phases between respiratory, blood pressure, and cardiac oscillations, at the specific so-called resonant frequency. We will explain how these physiological modifications are at the basis of an increase in heart rate variability (HRV) through vagal efferent enhancement, which is likely the origin of multiple peripheral and central benefits.

II- Central and reflex interactions involved in heart rate variability

HRV is under the control of the ANS (Hedman et al., 1995). The ANS, from an anatomical point of view, is divided into two parts: the craniosacral, or parasympathetic, and the thoracolumbar, or sympathetic. The sympathetic and parasympathetic components of the ANS are also known as the "fight-or-flight"

(characterized by an increase in heart rate) and ”rest and digest” (characterized by a decrease in heart rate) systems (Benson et al., 1974; Shekhar and DiMicco, 1987). However, HRV is mainly under the control of the vagal parasympathetic nervous system, given that the sympathetic outflow on the heart is too slow to elicit beat-to-beat changes (Jose and Collison, 1970).

Over the past few decades, following the publication of HRV guidelines by the Task Force in 1996 (Task Force 1996), the importance of vagally-mediated HRV (vmHRV) has steadily increased (Kleiger et al., 2005; Laborde et al., 2017). In separate proportional hazards regression analyses that adjusted for relevant risk factors, a higher vmHRV was found to be associated with higher life expectancy (Piccirillo et al., 2001, 1998). In addition, greater cognitive flexibility (Colzato et al., 2018), resilience to stress (Hirten et al., 2020), or resistance to temptation in dietary challenges (Maier and Hare, 2017), were also observed in patients with higher vmHRV. These findings illustrate the relevance of vmHRV as a marker positively related to health, wellbeing, and self-regulation.

VmHRV can be indexed by parameters in the time-domain and in the frequency-domain. Parameters within the time-domain include examples such as the root mean square of successive differences (RMSSD), or the respiratory sinus arrhythmia (RSA), calculated as the difference between the maximum and minimum cardiac interbeat interval per breath (Berntson et al., 1997). Regarding the frequency-domain analysis, HRV can be divided into two major frequency domains (low- and high-frequency domains) (Task Force, 1996), and both may depict vmHRV depending on the respiratory rate, as detailed below.

II-1- The low-frequency band (0.04-0.15 Hz)

The analysis of the low frequency band was previously thought to be a pure estimation of sympathetic activity. Experiments in 1965 were the first to suggest a spinal genesis for oscillations in the low-frequency band (Fernandez de Molina and Perl, 1965). In decerebrate-vagotomized cats (cats with abnormal posture who underwent a surgical operation in which cerebral brain function was removed and one or more branches of the vagus nerve were cut), a peak at approximately 0.1 Hz was found in the spectral profile of systolic blood pressure, sympathetic nerve activity, but also heart rate, suggesting that cardiac oscillations at this frequency rely, at least in part, on sympathetic modulation (Montano et al., 2000). Pagani and collaborators found that a bilateral stellectomy (i.e., surgical excision of the stellate ganglion) in dogs was able to abolish any sympathetic-induced increase in cardiac low-frequency power (normalized units) (Pagani et al., 1986). An observation in quadriplegic patients, whilst in a resting supine position, found the low-frequency peak to be absent, suggesting that it was caused by the interruption of the spinal pathways linking supraspinal cardiovascular centers with the peripheral sympathetic outflow (Inoue et al., 1990). On the contrary, Grasso et al. (1997) concluded that all fluctuations in the R-R low-frequency peak exclusively resulted from changes in the parasympathetic nervous system and failed to note any postural influence on the sympathetic nervous system (Grasso et al., 1997). However, using pharmacological manipulations with a beta-adrenergic receptor antagonist (propranolol) to induce a blockade of sympathetic activity, and/or a muscarinic cholinergic receptor antagonist (atropine) to abolish vagal activity, Houle and Billman observed that the low-frequency component of the heart rate power spectrum may actually result from an interaction of the sympathetic and parasympathetic nervous systems (Houle and Billman, 1999).

Given the discrepancies noted above, there may be an explanation that might account for some of the heterogeneous findings. It appears that restricting the sympathetic frequency band to 0.05 Hz and 0.1 Hz results in the best sympathetic indicator. While the frequency range of 0.10-0.15 Hz has a significant negative correlation with heart rate, suggesting a stronger parasympathetic influence in this range (Jaffe et al., 1994). A phenomenon called “baroreflex resonance” accounts for the vagal influence in this range, at approximately 0.1 Hz (Kromenacker et al., 2018; Vaschillo et al., 2002, 2006), and is described as a ‘‘negative feedback’’ system with a constant delay (Lehrer, 2013). Both heart rate and blood pressure vary in a closed-loop so that a change in either function causes a change in the other. When carotid and aortic baroreceptors are activated following an increase in mean arterial pressure, vagal and glossopharyngeal afferents are stimulated and send inputs to baroreceptor-second order neurons in the nucleus of the tractus solitarius (located in the lower dorsal brainstem) (Housley et al., 1987; Norcliffe-Kaufmann, 2019) (Figure 1). Cardiac vagal motor neurons in the ventral medulla (located mainly in the nucleus ambiguus) (McAllen and Spyer, 1978) are then stimulated and subsequently produce a reflex decrease in heart rate following the release of acetylcholine (ACh) by vagal parasympathetic efferents onto the heart (baroreflex cardiac response) (Fritsch et al., 1991; Guyenet et al., 1987) (Figure 1). This bradycardia buffers the initial increase in blood pressure. On the contrary, a decrease in blood pressure will halt baroreceptor activity, and heart rate will increase. However, heart rate and blood pressure reaction shifts are not instantaneous. For one stimulus that increases heart rate, the resulting increase in blood pressure (due to an increase in the quantity of blood circulating during each cardiac pulse) is delayed by approximately five seconds, because of inertia and plasticity in the blood coursing through the vascular system (Vaschillo et

al., 2006) (Figure 2A). In response, the baroreflex cardiac response occurs within a fraction of a second after blood pressure starts to change. Again, this decrease in heart rate produces a decrease in blood pressure with an approximate delay of five seconds, which in turn immediately increases heart rate through the vagally-mediated baroreflex. In total, for one pressure stimulus, heart rate oscillates approximately every ten seconds. In the absence of other stimuli, the cardiac oscillations will decrease with time and eventually disappear (Lehrer and Vaschillo, 2008; Lehrer et al., 2000; Vaschillo et al., 2006) (Figure 2B). Thus, the "baroreflex resonance" is generally composed of 0.1 Hz oscillations.

It is important to note that the length of the delay (inertia) differs slightly across individuals and ranges between 4–6.5 seconds; i.e. the natural frequency of these oscillations is actually between 0.075–0.12 Hz (Vaschillo et al., 2006). These values seem dependent on height (lower in taller men) due to an effect on vascular inertia, but not age or weight (Vaschillo et al., 2006). Therefore, it may be important to estimate the individual "baroreflex resonance" frequency before the realization of SPB, using HRV-biofeedback (called HRV-BF). In HRV-BF, the participants may be asked to reduce their breathing rate [usually but not necessarily at 6 cpm precisely] until they reach the lowest heart rate at expiration (Lehrer and Vaschillo, 2008). Alternatively, HRV-BF may help to find the resonance frequency by identifying the breathing rate between 4.5 and 6.5 cpm, optimizing the following criteria: LF-HRV, amplitude of the LF spectral peak, average peak-to-trough amplitude, and phase synchrony between heart rate and breathing (Fisher and Lehrer, 2021; Lehrer et al., 2000).

Other vagally-mediated cardiac oscillations may arise at 0.1 Hz from the tonic vagal baroreflex activation to buffer Mayer waves (Julien, 2006). These blood pressure oscillations, with a 10-second periodicity, are tightly coupled with synchronous

oscillations of efferent sympathetic nervous activity and are almost invariably enhanced during states of sympathetic activation (Julien, 2020).

II-2- The high-frequency band (0.15-0.40 Hz)

Respiration influences both heart rate and blood pressure. It is suggested that the high-frequency domain of HRV largely reflects the respiratory gating of the output of the vagus nerve on the sinoatrial node of the heart (Saul et al., 1990). During inspiration, the efferent vagal outflow is reduced by the direct action of central respiratory neurons (CRN, located in the lower ventral medulla) on vagal motor neurons, and sympathetic efferents are stimulated to increase heart rate (Berntson et al., 1997; Eckberg, 2003, 1983; Feldman and Ellenberger, 1988). In contrast, during expiration, vagal outflow is restored and heart rate decreases. Respiratory-induced cardiac oscillations are “in phase” (0°) with the respiratory flow, but this is not simultaneous: there is a time delay of a few seconds for cardiac oscillations (no temporal coherence with respiration) (Laude et al., 1993) (Figure 3A).

Respiratory-induced pressure oscillations result largely from the mechanical interaction between respiration and cardiac output (Figure 4) (Montano et al., 2000). During each inspiration and increase in negative intrathoracic pressure, a rapid increase in venous return in the right ventricle associated with a decrease in cardiac output occurs, leading to an associated decrease in arterial pressure (Verhoeff and Mitchell, 2017). These oscillations, called Traube-Hering waves, are “out of phase” (180°) with the respiratory flow (Billman, 2011). Because of the tonic activation of the baroreflex (see above), vagal cardiac oscillations immediately compensate for these vascular pressure changes. The resulting cardiac oscillations are at 180° with blood pressure oscillations and thus “in phase” (0°) with respiratory changes (Figure 3A). To

note, Traube-Hering blood pressure-induced cardiac oscillations are synchronous (no delay) with respiration (Laude et al., 1993).

The resulting cardiac oscillations are called RSA. They are low because both direct (induced by CRN activation) and indirect (baroreflex-induced Traube-Hering waves) respiratory-induced influences are shifted one from the other (not coherent). For most people, RSA at spontaneous breathing frequency is between 0.15 and 0.4 Hz (Tortora and Derrickson, 2020), defining the limits of the high-frequency vmHRV domain (Task Force, 1996). Vagal origin for RSA have support in this range as studies found that RSA is drastically attenuated or even completely eliminated after administration of atropine, a muscarinic receptor blocker (Pagani et al., 1986; Pomeranz et al., 1985), or in vagotomised cats (Montano et al., 2000).

Vagally-mediated RSA can be modulated by superior central influences through their actions on vagal motor neurons. For example, direct and indirect influences of central structures involved in stress, like the dorsomedial nucleus of the hypothalamus (DiMicco et al., 2002; Sévoz-Couche et al., 2013, 2003; Sévoz-Couche and Brouillard, 2017), decrease the baroreflex gain and reduce the tonic baroreceptor drive on vagal motor neurons. This results in the diminution of the basal level of vagal activity and therefore the decrease of RSA (Brouillard et al., 2020, 2019; Sévoz-Couche et al., 2013, 2003). In addition, stress increases sympathetic activity that has a negative influence on parasympathetic tone because RSA is slightly enhanced by atenolol or propranolol, two beta-adrenergic receptor blockers in humans (Pagani et al., 1986; Pomeranz et al., 1985; Taylor et al., 2001), though this result could not be reproduced in rats (Pereira-Junior et al., 2010). To note, RSA is not only affected in diseases linked to stress but also in pathological conditions with vagal inhibition like Parkinson's

disease (Li et al., 2021), diabetes, and obesity (Liao et al., 2017; Rosengård-Bärlund et al., 2011), or frailty (Katayama et al., 2015).

When summarizing the data during spontaneous breathing, cardiac oscillations between 0.15-0.40 Hz are vagally-mediated and in phase with respiration, through direct (following medullary cardiorespiratory rhythm generator activation, delayed responses) and indirect (following baroreflex activation by Traube-Hering waves, responses not delayed) influences (Figure 4).

III- SPB & RSA

Breathing is suggested to be the origin of RSA; therefore, RSA amplitude is modified by respiratory frequency. An increase in respiratory frequency leads to a progressive decline in RSA as vagal effectors become less able to follow higher frequency variations (Berger et al., 1989). On the contrary, a reduction in the breathing rate can increase RSA. To avoid hypoventilation and maintain minute ventilation (VE), tidal volume (Vt) must increase when respiratory frequency (f) decreases, given that VE=Vt*f. Hence, SPB is usually associated with deep (but not forced) changes in thoracic volume. When the breathing rate is below 0.15 Hz, RSA is found in the low-frequency domain (Kromenacker et al., 2018). Kromenacker and colleagues (2018) showed that HRV power across the low-frequency range was found to be nearly eliminated by the parasympathetic blockade during SPB, while similar spectral power during sympathetic blockade and placebo was statistically indistinguishable, reinforcing the fact that RSA is vagally-mediated even during SPB.

Effects of SPB on RSA and cardiac oscillation amplitude

Regarding the effects of SPB on RSA and cardiac oscillation amplitude, Hirsch and Bishop showed that RSA increased regularly as the breathing rate diminished

until a plateau was reached at approximately 0.1 Hz (6 cpm) (Hirsch and Bishop, 1981). They also observed that RSA is influenced by respiratory volume (RSA at 0.1 Hz was higher for a tidal volume of 3 l than for 0.5 l). However, after RSA normalization for tidal volume, they found that normalized points fell within two-SD of the 1 l curve and concluded that the system behaved as a linear function over the entire frequency range from 0.4 to 0.1 Hz, but not below. Accordingly, an increase in total HRV (including RSA amplitude) was observed during SPB (6 cpm) compared with spontaneous breathing (between 0.1 and 0.2 Hz) and paced breathing at 0.2 Hz (Tsai et al., 2015). RSA amplitude depends on the variation in cardiac oscillations. The calculation of maximal cardiac (deltaHR) changes during acute SPB seems to be more sensitive to indicate an increase in cardiac vagal activity than the usual HRV analyses (e.g., RMSSD) (Löllgen et al., 2009) or classic autonomic tests (Izzi et al., 2018).

The increase in RSA and deltaHR during SPB is a reflection of the increase in vagal activity

The increase in RSA and deltaHR at 6 cpm reflects an increase in vmHRV through higher variability (through an increase in the difference [increase in variability] between successive values in the heart signal). In support of this hypothesis, Poincare plots (showing the relationships between two successive RR interval values) and RMSSD (which evaluates short-term changes) are both increased during SPB (Guzik et al., 2007; Laborde et al., 2021). While the cardiac waveform aspect during spontaneous breathing appears to be more irregular (which would indicate a healthier heart) than during SPB, there is actually an increased entropy during SPB (Mary et al., 2018; Liu et al., 2021; Matić et al., 2020). Therefore, the sine wave-like HRV waveform during SPB appears more ordered visually; however, concerning HRV

parameters, they are actually more complex and unpredictable than during spontaneous breathing, and cardiac adaptation to respiration changes is higher.

Importantly, the inhalation/exhalation pattern of SPB may matter concerning vmHRV. A body of evidence demonstrates that at a constant respiratory rate, an equal or lower inspiratory/expiratory time ratio that emphasizes exhalation length, was shown to increase vmHRV parameters in comparison to a higher ratio, as seen in European and North American studies (Bae et al., 2021; Edmonds et al., 2009; Jafari et al., 2020; Laborde et al., 2021; Van Diest et al., 2014). Similarly, in another study involving healthy European participants, both symmetrical (equal ratio of inhaling/exhalation timing, e.g. 5:5) and skewed (exhalation longer than inhalation, e.g. 4.5:5.5) breathing patterns were seen to have similar positive effects on vmHRV compared to baseline (De Couck et al., 2019). In another study, Hungarian volunteers performed short breathing sessions at 6 cpm with either equal or different inspiratory/expiratory ratios (5:5, 3:7, and 7:3 inspiration expiration ratios) (Paprika et al., 2014). VmHRV parameters and baroreflex sensitivity increased significantly during each SPB pattern compared to baseline, but none of these parameters differed significantly across the different inspiratory-expiratory patterns (Paprika et al., 2014). The authors suggested that the major determinant of autonomic responses induced by SPB may be the breathing rate itself rather than the inspiratory-expiratory pattern. It was also suggested that, in addition to a slow-paced and deep breathing pattern, a pause (>1 sec) between inspiration and expiration could increase RSA more dramatically (Edmonds et al., 2009; Russell et al., 2017). However, the duration of the pause may play a role, given that a 0.4s pause after inhalation and after exhalation did not provoke an increase in vmHRV (Laborde et al., 2021). Therefore, we suggest **at least four mechanisms** that are involved in vagal activity increases during SPB

(reflected by a maximal RSA). This integrates the notions of the coherence of phases between respiratory, blood pressure, and cardiac oscillations, at 0.1 Hz:

Firstly, as described above (see p.8), cardiac oscillations at 0.1 Hz originating from the baroreflex resonance (induced by any pressure change) normally decrease with time and eventually disappear. However, during SPB, because breathing stimulation is sustained at 0.1 Hz, sustained cardiac oscillations occur simultaneously to those normally observed as a result of the "baroreflex resonance" and therefore decreases are not present (no reduction of amplitude with time) (Figure 5).

Secondly, if there is a delay between respiratory and cardiac oscillations during spontaneous breathing (see p 8), this delay diminishes as the breathing rate decreases (Laude et al., 1993) and disappears when the breathing rate reaches approximately 0.1 Hz (Lehrer and Gevirtz, 2014). So, during SPB, heart rate oscillates at 0.1 Hz from either the direct influence of central respiratory generators or the baroreflex response to both Traube-Hering (frequency-dependent of the respiration) and Mayer waves (always at 0.1 Hz, independent of the respiration). To note, this exact coherence at 0.1 Hz is especially obtained in young participants, suggesting that cardiovascular characteristics of older people may affect the phase relationship (Lehrer et al., 2020). As a result, all cardiac oscillations are produced exactly in phase (coherence), reinforcing each other. In addition, the lower the difference between natural and manually applied frequencies of the body, the higher the amplitude of the forced vibrations. Essentially by slowing breathing rate, we are coupling our respiratory and cardiac rhythms, and this phenomenon is known as the resonant frequency. Accordingly, when the breathing rate is 0.1 Hz, all natural and applied cardiac oscillations appear at equal frequencies, and the amplitude of applied cardiac oscillations is maximal. This is why 0.1 Hz can be generally called a "resonant

frequency", even if it remains relevant to estimate the individual resonant frequency before the realization of SPB because, as written above, the "baroreflex resonance" may differ from 0.1 Hz within a group of participants (Vaschillo et al., 2006).

Thirdly, heart rate values during spontaneous breathing change rapidly and the time for vagus nerve stimulation (1-2 seconds of expiration per breathing cycle) doesn't allow ACh to be completely released (which needs approx. 2 seconds) and then hydrolyzed (which needs approx. 2 seconds) before the next breathing cycle (Baskerville et al., 1979; Eckberg and Eckberg, 1982). Thus, the effect of ACh on the heart is of short duration. In the case of SPB at the resonant frequency (5.5 cpm [0.09 Hz] or 6 cpm [0.1 Hz], (Vaschillo et al., 2006)), exhalation lasts approximately 5 sec in both cases, and this length of time seems ideal for ACh's complete release and hydrolysis during each breathing cycle, to allow a perfect turnover (Figure 3B). Vagal action on the heart is then deemed "maximal", which is shown by a large RSA peak (high vmHRV).

A fourth explanation may also account for the improvement of vagal activity during SPB. Central respiratory generators are modulated by lung stretch receptor activation during large inspiration to inhibit medullary inspiratory neurons and start expiration (Loewy and Spyer, 1990; Moreira et al., 2007), and this phenomenon may influence RSA amplitude. Recently, Noble and Hochman (2019) suggested that there was a preferential recruitment of slowly-adapting pulmonary afferents during prolonged inhalation, as in slow-paced and deep breathing, to improve exhalation (Noble and Hochman, 2019). However, direct central neural mechanisms seem crucial, as no RSA can be observed in a transplanted heart until autonomic reinnervation (Sands et al., 1989). Intra-cellular recordings of vagal motor neurons reveal a close association between the postsynaptic potential that occurs in phase

346 with phrenic nerve activity and is independent of lung inflation (Gilbey et al., 1984),
347 indicating a major direct action of the central respiratory generator on vagal
348 cardiomotor neurons.

349 *The maximal increase in RSA or deltaHR depends on age and gender, but not*
350 *on the ethnic origin*

351 Reduced baroreflex sensitivity is associated with aging (Monahan, 2007). This
352 may explain why the maximal RSA obtained during SPB depends on age (Hirsch and
353 Bishop, 1981; Reimann et al., 2010). RSA during SPB at 6 cpm is high in participants
354 below 30, then decreases for participants between 30 and 40, and reaches a plateau
355 for people above 40 (Hirsch and Bishop, 1981). Older participants were shown to have
356 increased vmHRV during SPB compared to spontaneous breathing (Reimann et al.,
357 2010), and an increase in baroreflex sensitivity during a few minutes of slow breathing
358 was also be observed in European and US patients with lower baroreflex sensitivity
359 (Calcaterra et al., 2013; Rosengård-Bärlund et al., 2011). These results show that
360 increases in vagal activity can be achieved during SPB even in patients with
361 dysautonomia.

362 Pre-menopausal women have higher functionality of the vagus nerve and
363 baroreflex sensitivity than young men during spontaneous breathing, and this
364 difference remains during SPB (Reimann et al., 2010). However, no difference was
365 observed between older men and women during spontaneous breathing or SPB
366 (Reimann et al., 2010). Another study from Germany found that RSA amplitude was
367 reduced in association with age, but independently of gender (Gautschy et al., 1986).

368 It appears that there is no difference in maximal cardiac changes during SPB
369 between multi-ethnic or multi-origin groups. DeltaHR during SPB did not differ in

Bangladeshi and European participants (Rahman et al., 1991), and RSA increased threefold during voluntary SPB in nine black and nine white healthy male South African volunteers (du Plooy and Venter, 1995). However, within our current knowledge, no specific study comparing young and old participants in multi-ethnic groups has ever been conducted, and further research on this topic is necessary.

As we reviewed above, SPB can produce an increase in vagal activity, an increase in baroreflex sensitivity, and larger cardiac oscillations. These phenomena may be at the origin of multiple beneficial effects, at peripheral and central levels.

IV- Slow-paced Deep Breathing positive effects

1- Peripheral benefits

Cardiovascular improvements: heart rhythm, blood pressure, and oxygen saturation

During SPB, when breathing frequency is around 0.1 Hz, cardiac oscillations are in phase (0^{o}) and have no delay with respiration; they are also out of phase (180^{o}) without delay with Traube-Hering and Mayer blood pressure oscillations. Under this conformation of temporal coherence between all waves, during each individual deep expiration, the heart immediately responds (no delay) to blood pressure increases by stark decreases in heart rate and vagal baroreflex sensitivity (Dick et al., 2014).

An alteration in autonomic balance, especially a reduced parasympathetic component, has been acknowledged to be a precursor to life-threatening cardiac events in cardiovascular diseases (La Rovere et al., 2003; Zuanetti et al., 1996), but is also a factor in several diseases, including mood disorders (Davydov et al., 2007; Lathers and Schraeder, 2006). In a study on a cohort of patients in a Public Mental Health Hospital in the US, the principal cause of death in patients with major depression was reported to be heart disease, with sudden cardiac death accounting for most of the

cases (Miller et al., 2006). In the same manner, we and others found that an animal model of psychosocial stress leads to a vulnerability to persistent autonomic dysfunction, cardiac hypertrophy, and ventricular ectopic beats, but only in the group of animals associated with persistent low vagal temporal and frequential parameters in HRV (Brouillard et al., 2020; Sgoifo et al., 1998). More specifically, a parasympathetic recovery in resilient animals is a sign of protection against cardiac events (Brouillard et al., 2020). This supports the potential beneficial effects of SPB on cardiac events during stress episodes, with a better balance in autonomic innervation. According to this hypothesis, a study reported a beneficial effect of a daily practice of SPB (6 cpm) on the frequency of premature ventricular complexes (PVC) in Indian women, though only in five of a series of 10 consecutive patients with frequent (≥10/minutes) unifocal PVC (Prakash et al., 2006). It is also suggested that SPB may be at the origin of ventricular synchrony (Dadu and McPherson, 2013).

When examining vascular pressure, systolic blood pressure decreases during acute (a few minutes) SPB practice in healthy participants (Dick et al., 2014) or during chronic (8 weeks) practice in American patients with hypertension (Bertisch et al., 2011). SPB also induces a reduction in blood pressure in healthy lowlanders (from Italy) exposed to acute or prolonged high altitudes (Bilo et al., 2012). However, these studies did not compare slow breathing to other interventions. This comparison is very important to estimate the part of distraction in the beneficial effect of SPB. Actually, in a participant blinded, multi-centre, randomised controlled trial was conducted in which the participants in the intervention group (IG) practiced deep breathing exercises guided by sound cues while those in the control group (CG) listened to the music during 8 weeks, both IG and CG interventions were associated with a clinically significant reduction in blood pressure. Importantly, deep breathing exercises did not

augment the benefit of music (Kow et al., 2018). Though an improvement in baroreflex sensitivity during SPB can explain the results on systolic blood pressure, it can't be excluded that it could partly be the consequent reduction in sympathetic activity (Harada et al., 1997). SPB at 6 cpm is also associated with attenuated autonomic responses to hypoxic stress (i.e., chemoreflex, increase in blood pressure and heart rate), increases in vmHRV, and preservation of baroreflex sensitivity in healthy Italian (Bernardi et al., 2006, 2002) as well as in Indian patients (Mourya et al., 2009) exposed to higher altitudes and in patients with heart failure and hypertension, respectively.

When examining oxygen saturation in Malaysian patients, increases were observed during 5, 7, or 9 minutes of slow-paced deep breathing (Cheng and Lee, 2018). According to the same line of argumentation, healthy lowlanders exposed to acute or prolonged high altitude had an increase in ventilation efficiency during deep breathing, as shown by the significant increase in blood oxygen saturation (reduction in the alveolar arterial PO_2 difference consistent with improvements in ventilation-perfusion mismatch), and reduced dead space minute ventilation during SPB (Bilo et al., 2012). This is consistent with animal experiments that reported a model simulating RSA that gas exchange at the alveoli is most efficient when heart rate starts increasing at the beginning of inhalation and starts decreasing just as exhalation starts, i.e., at an exact 0◦ phase relationship (Hayano et al., 1996). It is noteworthy that nose breathing alone also imposes approximately 50 percent more resistance to the air stream, as compared to mouth breathing (Cottle, 1958). This results in 10 to 20 percent more oxygen uptake. Nasal breathing, as opposed to mouth breathing, increases circulating blood oxygen and carbon dioxide levels, and improves overall lung volumes.

Exercise performance

443 It is also important to consider the role of SPB in relation to exercise. Reduced vmHRV
444 is associated with lower exercise performance and maximal oxygen consumption
445 during exercise (VO_{2max}) (Boutcher et al., 1997). An increase in VO_{2max} is a result of
446 two physiological adaptations, one being an increase in the difference between arterial
447 and venous oxygen content (i.e., the amount of oxygen from each ml of blood
448 transported to and consumed by the tissue), and the second being an increase in
449 cardiac output during exercise (Meyer et al., 1994). SPB may impact VO_2max due to
450 the activation of pre-ganglionic parasympathetic vagal neurons in the medulla,
451 provoking an augmented contractile response to sympathetic stimulation during
452 exercise through the downregulation of G Protein-Coupled Receptor Kinase 2 (GRK2
453 gene) and an arrest in expression in left ventricle myocytes to increase cardiac output
454 (Machhada et al., 2017). Accordingly, SPB realization over a few weeks improved
455 physical performance and increased VO_2max (and decreased skin conductance, a
456 reflection of sympathetic activity) in Indian basketball players (Choudhary et al., 2016),
457 as well as increased peak running velocity and VO_2 in runners from New-Zealand
458 (Caird et al., 1999).

459 *Muscle strength, oxidative stress, and inflammation*

460 Reduced vmHRV is also associated with muscle weakness (Reis et al., 2014).
461 Previous evidence found that skeletal muscle fatigue or dysfunction correlated with
462 inflammation and oxidative stress in the diaphragm muscle in chronic obstructive
463 pneumopathy disease (COPD) (Heidari, 2012; Supinski et al., 1993). Four weeks of
464 reduced breathing (with respiration holding) in Thai COPD patients with mild to
465 moderate symptoms, improved peak inspiratory pressure (via measuring the
466 respiratory muscle strength), and six-minute walking distance (Leelarungrayub et al.,
467 2018). This intervention also reduced TAC (an oxidative stress marker), as well as IL-

6 but not TNF-α (inflammatory markers) (Leelarungrayub et al., 2018). In another study lasting three months, using device-guided SPB for a respiration rate of 6 cpm, a significant continuous decrease in mean blood pressure associated with reduced levels of blood pro-inflammatory cytokines (including TNF-α) was found in patients from Taiwan suffering from hypertension (Wang et al., 2021). The findings suggest that SPB realized exactly at 6 cpm may have a stronger effect on inflammation than a non-controlled reduction in breathing rate. This hypothesis should be interpreted with caution, as another study found no effect of HRV-BF on inflammation. The HRV-BF group showed significant attenuation of the LPS-induced decline in HRV for the 6 hours following LPS exposure. HRV-BF also reduced symptoms of headache and eye sensitivity to light following lipopolysaccharide (LPS) exposure, but did not affect LPS-induced levels of pro-inflammatory cytokines or symptoms of nausea, muscle aches, or feverishness (Lehrer et al., 2010).

The mechanism involved in the potential anti-inflammatory effect of SPB may involve vagal stimulation. This has been extensively described in Tracey et al. (2002). Besides humoral and cellular regulation, neural regulation is required for the host to fight against pathogens and resolve inflammation (Tracey, 2002). Electrical stimulation of the vagus nerve can trigger the synthesis of ACh in the spleen. Splenic macrophages express α7 nicotinic ACh receptors, which are activated by ACh to suppress the activation of pro-inflammatory cytokines (Reid, 2008; Smith and Reid, 2006), and this modulatory mechanism is termed the Cholinergic Anti-inflammatory Pathway (CAP). Vagus nerve endings are also reported to innervate the distal airways of the lung, even in the alveoli (Fox et al., 1980; Hertweck and Hung, 1980), explaining the possible mechanisms of SPB's influence on inflammation in respiratory diseases as discussed above.

2- Central benefits

Heart rate and blood pressure are both influenced during respiration (Figure 4) (Dick et al., 2014; Saul et al., 1990). During SPB, a breathing cycle lasting five seconds during each inspiration and each expiration results in a five-second cycle of continuous change in mean blood pressure (a five-second decrease followed by a five-second increase, respectively). The amplitude of these five-second pressure oscillations increases because of a larger thoracic pressure change during SPB compared to spontaneous breathing, and also because of larger respiratory-induced cardiac oscillations (Barnett et al., 2020). Consequently, the amplitude of each blood pressure oscillation during SPB is long and maximal, and thus, because of baroreceptor activation, vagal inputs reaching the brain are stronger and last longer than during spontaneous breathing. Increases in vagal inputs to these brain areas may enhance activation within several brain regions; these influences may also be reinforced by the fact that large cardiac oscillations seem to modify cerebral blood flow in these regions, and synchronize them (Mather and Thayer, 2018; Smith et al., 2017) (Figure 6).

Among these regions, physiological evidence in rodents indicates that visceral and cardiorespiratory vagal inputs directly or indirectly activate diverse regions of the prefrontal cortex in the left hemisphere, including the insula and cingulate cortex, as well as limbic regions (Penfield and Faulk, 1955; Saper, 2002). These findings suggest that SPB may durably (five second cycle) increase connectivity and activate these prefrontal and limbic regions, to produce positive central effects.

Theoretically, these findings enable us to integrate the effects of SPB within the neurovisceral integration model (Smith et al., 2017; Thayer et al., 2009). This model is based on the central autonomic network (Benarroch, 1993), a functional network

encompassing the brain areas responsible for the functioning of the autonomic nervous system. Accordingly, similar brain structures are involved in the regulation of emotional, cognitive, and cardiac processes. The neurovisceral integration model further suggests that vmHRV, representing the output of the central autonomic network, reflects the effectiveness of emotional, cognitive, and cardiac regulation. Crucially, the relationship between the heart and the brain is suggested to be bidirectional (Thayer and Lane, 2009). This bidirectional connection can be used as a leverage mechanism for techniques that aim to influence the central autonomic network, such as SPB. Based on the current evidence, we may suggest a neurovisceral integration in which the effects of SPB on vagal afferents get integrated within the central autonomic network (Benarroch, 1993), before being reflected in the activity of vagus nerve efferents (Smith et al., 2017).

NeuroPhysiological effects of SPB:

Modifications in functional magnetic resonance imaging (fMRI)

A fundamental relationship between neural activity, blood flow, and metabolism was postulated in 1890 (Roy and Sherrington, 1890). Later, fMRI was developed and allows for measuring brain activity by detecting changes associated with blood flow (Budinger and Lauterbur, 1984). Using this technique, after an HRV-BF intervention (five training sessions per week for 8 weeks), functional connectivity of the ventromedial left prefrontal cortex increased mainly with the insula, the amygdala, the middle cingulate cortex, and lateral prefrontal regions when compared to changes in the control group (Schumann et al., 2021). An increased activity showed by other fMRI data during SPB relative to spontaneous rate breathing was observed within prefrontal regions, including the insula and the cingulate cortex (Critchley et al., 2015).

Modifications in blood-oxygen-level-dependent (BOLD) signals

VmHRV is significantly associated with increased regional cerebral blood flow in the prefrontal cortex (including left insula), but also in the left sublenticular extended amygdala/ventral striatum (Mather and Thayer, 2018; Thayer et al., 2012). A strong phase coupling of heart rate interval and BOLD oscillations has been observed in the left mid-cingulate and posterior cingulate regions as well as in the amygdala, at the resonant frequency (0.1 Hz) (Pfurtscheller et al., 2017). Similarly, deep (increase in tidal volume due to change in thoracic volume) breathing induces an increase in BOLD activity in left insular and cingulate areas (Critchley et al., 2015). Another analysis of BOLD signals during the display of positive and negative images suggested that SPB increases anterior insular and cingulate activity in the left hemisphere in association with positive images (correlated with an increase in vmHRV) while the right hemisphere was correlated with negative images and a decrease in vmHRV (Strigo and Craig, 2016). It is noteworthy that gender may have an impact on the lateralization of either positive or negative emotion processing: in males, emotional stimuli predominantly activated the left anterior/mid-insula and right posterior insula, whereas in females, emotional stimuli activated bilateral anterior insula and the left mid and posterior insula (Duerden et al., 2013). These findings suggest that SPB may have different effects on emotions depending on gender.

Modification in EEG frequency bands

Modulation in EEG has also been found to be in line with SPB. The frontal theta power, a mechanism for attention and cognitive control (Cavanagh and Frank, 2014; Gongora et al., 2015), was significantly larger in participants realizing SPB for five to nine minutes in comparison to controls (Cheng et al., 2018). In the same study, the

mean power of the alpha and beta bands - involved in anxiety control (Mennella et al., 2017; Pavlenko et al., 2009) - was reduced compared with the control group, even at a seven-day follow-up (Cheng et al., 2018). It is important to note that respiration itself, via sensory inputs from the olfactory bulb, modulates neuronal oscillations in the delta and gamma frequency bands in the neocortex of awake mice (Ito et al., 2014), and respiration through the nose but not the mouth synchronizes electrical activity in the human piriform (olfactory) cortex, as well as in limbic-related brain areas, including the amygdala and hippocampus (Zelano et al., 2016).

In summary, it can be inferred that nasal slow respiration modulates neuronal oscillations and cerebral blood flow (and therefore activity) in different central regions, especially in the prefrontal cortex and limbic areas (Jelinčić et al., 2021), which can potentially induce several psychological benefits.

Neuropsychological effects of SPB

Pain sensation regulation

Several studies suggest a link between SPB and pain ratings. When practiced acutely (2 min) (Chalaye et al., 2009) or chronically (4 weeks) in US veterans suffering from chronic back pain (Berry et al., 2014), both SPB and HRV-BF were effective in reducing perceived pain. Similar results were found in both American men and women with fibromyalgia syndrome (Reneau, 2020; Zautra et al., 2010), respectively. To note, the study by Reneau showed that the patients who completed the entire experiment with HRV-BF realized 20-minutes daily instead of the 20-minutes twice daily initially planned. These results may suggest that the duration of chronic SPB practice should not exceed 20 minutes to ensure better compliance. When comparing the effects of SPB and HRV-BF on pain, the mean detection and pain thresholds in young and

589 healthy undergraduate German students showed a significant increase resulting from
590 SPB without HRV-BF (6 cpm), but not with SPB with HRV-BF (Busch et al., 2012). So,
591 HRV-BF may add additional stress during biofeedback training, due to an increased
592 attentional load.

593 However, it is important to note that other studies could not reproduce the effects of
594 acute SPB on pain in healthy European people (Courtois et al., 2020; Zunhammer et
595 al., 2013). In a similar vein, German patients with chronic low back pain were
596 randomized to either HRV-BF or non HRV-BF (Kapitza et al., 2010). Both groups
597 performed daily 30-min home training for 15 consecutive days. Between-group
598 comparisons reached no significance considering pain levels, even if changes were
599 more pronounced in the HRV-BF condition, which was also true for the course of the
600 relaxation index.

601 It is possible that respiratory hypoalgesia may be the consequence of vagal afferent
602 activation, as previously discussed (Sévoz-Couche et al., 2002), with the activation of
603 the periaqueductal gray involved in pain processing (Ong et al., 2019). However,
604 another circuitry independent of the periaqueductal gray may be involved. As
605 discussed earlier, the left insula was activated during SPB (Critchley et al., 2015).
606 Zautra and collaborators (Zautra et al., 2010) suggested that SPB produces an
607 increased activation in the left mid-insula and the left anterior cingulate, to
608 counterbalance the acute activation in the right anterior insula involved in pain
609 processing (Brooks et al., 2002) by virtue of opponent interaction (Craig, 2005). In
610 addition, the insular cortex is involved in the salience network,
611 interoceptive awareness of body states, and attention (Taylor et al., 2009).
612 Gholamrezaei and collaborators estimated that SPB had no effect on pain through
613 vagal activation, but rather suggested that other mechanisms, such as attentional

modulation (distraction) may underlie this effect (Gholamrezaei et al., 2021b, 2021a). It is also likely that, because each experimental condition (control and SPB, with or without an inspiratory threshold load) was repeated four times in a randomized order, training/learning by re-exposure to the same task may also participate to the beneficial effect seen in these studies.

However, the effect of SPB on pain modulation may have multiple origins. SPB with a lower inspiratory/expiratory ratio was found to significantly attenuate pain more than paced breathing at a spontaneous frequency or SPB with a higher inspiratory/expiratory ratio (Jafari et al., 2020). The authors suggested that this hypoalgesic effect may be partially caused by the distractive effect and breathing awareness of voluntary changes in one's breathing pattern, but that beyond this effect, other mechanisms may contribute to the analgesic effect of SPB (Jafari et al., 2017).

Interoception: awareness, decision-making, and concentration

An increase in activity in left insular and cingulate regions during vagal stimulation (see above) suggests that interoceptive awareness and accuracy may be obtained during SPB. However, mixed results have been found on this matter. When a heartbeat discrimination task was presented before and after 20-minutes of either HRV-BF, SPB, or a control condition (viewing a film clip), a general tendency for improvement in heartbeat detection accuracy was reported across all intervention groups of German participants, but groups did not differ significantly (Rominger et al., 2021). These data suggest that distraction, more than a reduced breathing rate, may improve interoception accuracy. On the other hand, RSA and BRS during SPB (5 minutes) were found to positively correlate with increases in interoceptive accuracy (recognition of a tone synchronized or not with heartbeats) in American patients (Leganes-

638 Fonteneau et al., 2021). However, it is important to note that no control group was
639 used in that study, so a possible effect of distraction may again account for the
640 beneficial effect of SPB on interoception.

641 The anterior cingulate cortex is also involved in decision-making (Couto et al., 2014;
642 Ohira et al., 2010), suggesting that SPB may have a positive effect on making a choice.
643 Higher levels of self-control in decision making in diet challenge were correlated
644 positively with vmHRV (Maier and Hare, 2017). When watching an emotionally neutral
645 film (sham condition), practicing two minutes of SPB was found to improve correct
646 answers in a 30-minute challenging business decision-making task with multiple
647 choice answers (De Couck et al., 2019). In addition, after ten weeks and at a one-
648 month follow-up, SPB was still found to be associated with a decreased choice
649 response time and improved concentration in association with an increase in vmHRV,
650 in young Indian basketball athletes (Paul et al., 2012). Interestingly, watching a
651 motivational video did not affect the outcomes (Paul et al., 2012), so the reduction in
652 breathing seems to have been responsible for the changes observed.

653 *Cognitive improvement*

654 It has been observed that SPB can influence cognitive functions. Neuronal pathways
655 project from the insula to limbic regions including the hippocampus (Mufson et al.,
656 1981; Saper, 1982), potentially underlying the modulatory role of SPB on cognition.
657 Breathing through one's nose synchronizes oscillations in the olfactory piriform cortex
658 and secondary in the hippocampus (Zelano et al., 2016), through direct connections
659 (Nigri et al., 2013). Both acute or chronic practice of SPB and HRV-BF seem to
660 influence cognition. Acute SPB increases the learning and retention of motor skills in
661 healthy Indian patients (Yadav and Mutha, 2016). Compared to a passive condition

(watching a documentary), executive functions (Stroop interference accuracy, automated operation span score, and perseverative errors) were found to be improved in healthy German participants by a single 15-minute voluntary SPB session at 6 cpm guided via a respiratory pacer (Hoffmann et al., 2019; Laborde et al., 2019; Laborde et al., 2021). However, with the use of HRV-BF, an increase in attentional skills as measured by the Trail Making Test, but not in executive performance (at the difference between the studies mentioned above using SPB), was observed in American older adults after a longer training period (3 weeks) (Jester et al., 2019). Other studies found no effect of SPB or HRV-BF on that topic compared to controls or other interventions not based on breathing modulation. De Bruin et al. (2016) compared the effects of mindfulness meditation, HRV-BF, and physical exercise. They found that the three interventions were equally effective in improving attentional control and executive functions (EFs). However, in the HRV-BF condition, pre–post effect sizes of change for attentional control and for a global index of EFs were small. Further, between-group pre–post differences revealed that the physical exercise group improved more on attentional control than the BF group, with a small effect size (de Bruin et al., 2016). In addition, in 36 female electronic manufacturing operators, Sutarto et al. (2013) did not find any between-group (HRV-BF and controls) differences, neither for interference nor for attentional control, after the intervention (Sutarto et al., 2013).

Again, differences in positive outcomes may stem from the characteristics of the interventions used in the studies.

Addiction

Assuming that feelings (and awareness) are engendered in the insular cortex while motivations (and agency) are engendered in the cingulate cortex (Devinsky et al.,

686 1995; Harsay et al., 2018), the increase in interoceptive regions during SPB may be
687 the substrate for explaining positive effects on uncontrolled impulsivity and substance
688 abuse (Garavan, 2010). In American and European participants, compared to
689 “treatment as usual” SPB induced a reduction in alcohol, nicotine, and drug cravings,
690 independent of intervention duration (Eddie et al., 2014; McClernon et al., 2004;
691 Penzlin et al., 2015). Specifically, both chronic (three 20-minute sessions of training
692 per week over two weeks or 60-75 minute sessions each week for three weeks) HRV-
693 BF practice (Eddie et al., 2014; Penzlin et al., 2015) and acute SPB at 6 cpm (series
694 of deep breaths every 30 minutes during a four-hour session) (McClernon et al., 2004)
695 were found to produce these effects. Concerning food cravings, the results are more
696 mitigated. In a study using chronic (12 session) HRV-BF compared to control,
697 subjective food cravings related to a lack of control caused over-eating to decrease
698 from pre- to post-measurement in the craving-biofeedback group, but remained
699 constant in the control group. Moreover, only the craving biofeedback group showed
700 a decrease in eating and weight concerns (Meule et al., 2012). However, the same
701 group later found in a pilot study that current food craving decreased during an initial
702 resting period, increased during acute paced breathing, and decreased during a
703 second resting period when breathing was either 6 or 9 cpm (Meule and Kübler, 2017).
704 Although current hunger increased in both conditions, it remained elevated after the
705 second resting period in the 9 cpm condition only. Thus, breathing rate did not
706 influence specific food cravings, and SPB appeared to only have a delayed influence
707 on state hunger.

708 *Stress and anxiety*

709 Anxiety is a result of an increased anticipatory response to a potential aversive event,
710 which manifests itself in enhanced right anterior insular cortex processing (Paulus,

711 2013). Individuals with low versus moderate anxiety traits showed different anterior
712 insula activity for prediction certainty (Harrison et al., 2021). Similar to pain modulation,
713 SPB may increase activation in the left interoceptive areas to counterbalance
714 enhanced activation in the right hemisphere to reduce stress and/or anxiety.

715 In college students exposed to a 15 minute verbal guided SPB exercise (somatic
716 relaxation), salivary cortisol levels were lower in the treatment group than in the control
717 group (Dawson et al., 2014). Acute (30-minutes) practice of both controlled SPB and
718 HRV-BF resulted in a reduction in stress and state anxiety (and increased vmHRV) in
719 Australian musicians or American athletes before performing in public (Dawson et al.,
720 2014; Wells et al., 2012). On a chronic basis, SPB over ten days decreased anxiety in
721 Indian basketball players (Paul and Garg, 2012). Similar results were found after 21
722 days of HRV-BF in healthy male young athletes from Poland, where the mean anxiety
723 score declined significantly for the intervention but not for the control group
724 (Dziembowska et al., 2016). Comparably, three weeks of HRV-BF in older North-
725 American adults caused decreases in depression, as well as in state and trait anxiety
726 (Jester et al., 2019). SPB practiced over four weeks was also effective in reducing
727 stress, negative emotions, and physical activity limitations in US veterans (Berry et al.,
728 2014). Interestingly, HRV-BF across eight weeks was more effective at decreasing
729 anxiety than muscle relaxation in healthy Korean students (Lee et al., 2015). These
730 results suggest that reduced breathing influences anxiety levels. When assessing the
731 longitudinal effects of chronic HRV-BF (5-minute twice daily for five-weeks) within a
732 group of French students in sports science was compared to a control group,
733 interesting findings emerged (Deschodt-Arsac et al., 2018). Similar states of anxiety
734 were found in the experimental group immediately after the five-week training when
735 compared to the control group, but vagal autonomic markers were higher and anxiety

736 scores were lower among the experimental group twelve weeks later (Deschodt-Arsac
737 et al., 2018). Finally, when applied over six weeks, SPB also decreased anxiety and
738 depression ratings in bipolar Brazilian patients, and importantly, these positive effects
739 were still observed at a ten-week follow-up (Serafim et al., 2019). These results
740 suggest that SPB at 6 cpm or HRV-BF both reduce mood disorders and stress through
741 the action of breathing more than mere relaxation and that these effects may not be
742 instantaneous but last longer when training duration is increased.

743 To sum up, the findings mentioned above suggest that SPB performed over several
744 weeks may trigger long-lasting effects, but not in all domains.

745 **Conclusions**

746 The increase in RSA amplitude (power) obtained at the resonant frequency (~ 0.1 Hz)
747 during SPB or HRV-BF (most likely with an equal or lower inspiratory/expiratory ratio),
748 reflects maximal vagal activity and baroreflex improvement, through an ideal time for
749 release and hydrolysis of ACh. These effects are due to the temporal coherence (no
750 delay) of the respiratory, blood pressure, and cardiac phases.

751 These phenomena are at the origin of several peripheral positive effects, including an
752 increase in oxygen saturation, a decrease in blood pressure, and inflammation (Figure
753 6). In addition, the increase in cardiac oscillations during SPB increases vagal inputs
754 to the medulla and cerebral blood flow, which is reinforced by nostril breathing. This
755 conjunction of phenomena activates diverse central sites, including the left insular and
756 cingulate regions (Figure 6). Consequently, an improvement in pain regulation,
757 emotion awareness, cognitive abilities, and stress regulation seems to be observed in
758 numerous studies during SPB and in HRV-BF. In summary, the findings reported here
759 suggest that breathing at the resonant frequency may improve a large range of

760 physiological and psychological outcomes, which are independent of participant
761 characteristics. It is still important to highlight that some studies also report no effects.
762 Additionally, though controls (no intervention) were systematically compared to SPB
763 or HRV-BF, cautious interpretation of the suggested wide range of benefits induced
764 by these techniques is needed. A more generalized use of placebo, including paced
765 breathing at a spontaneous frequency or neutral interventions, would help to
766 disentangle the effects of SPB from those solely linked to breathing awareness or
767 distraction.

768

Figures captions

Figure 1. Schematic drawings of the central and peripheral pathways stimulated during slow-paced deep breathing

The central motor generators (pink circles), in the ventral lower medulla, influence the vagal motor nucleus. During expiration, medullary vagal cardiomotor neurons (located mainly in the nucleus ambiguous (purple circle) projecting to the heart (parasympathetic vagal efferents, representing 20% of total vagal fibers) are stimulated over five seconds to produce bradycardia through the release of acetylcholine. Long and strong parasympathetic activation is at the origin of the peripheral (including an increase in vmHRV) effects of SPB. At the same time, blood pressure increases over five seconds, and baroreceptors located in the carotid bifurcation and aortic arch are stimulated. Glossopharyngeal and aortic nerves originating from carotid and aortic baroreceptors (grey circles), respectively, run through vagal afferents (representing 80% of total vagal fibers). Vagal afferents reach the nucleus tractus solitarius (NTS, green circle) in the lower dorsal medulla. From the NTS, inputs are conveyed, directly or indirectly, to the prefrontal (insula) and cingulate cortex, which are reciprocally connected with limbic areas, i.e. the hippocampus and the amygdala. These connections are reinforced by orbitofrontal influences, especially those activated during nostril breathing. These pathways are at the origin of the central effects of SPB.

Figure 2: "Baroreflex Resonance" at 0.1 Hz

A. For one stimulus that increases heart rate, an increase in blood pressure occurs due to a rise in the quantity of blood circulating during each cardiac pulse. This response is delayed by five seconds, because of inertia and plasticity in the blood

coursing through the vascular system. In response, the baroreflex cardiac response occurs within a fraction of a second after blood pressure starts to change, and heart rate decreases. Again, this decrease in heart rate produces a mechanical decrease in blood pressure delayed by five seconds, which in turn immediately increases heart rate through the vagally-mediated baroreflex. In total, one cycle (oscillation) lasts approximately ten seconds (0.1 Hz) (bottom).

B. If only one stimulus occurs, cardiac oscillations at 0.1 Hz decrease throughout successive cycles, and eventually disappear.

Figure 3. The link between heart rate, blood pressure, and respiration

A- During spontaneous breathing, respiration flow oscillates at approximately 0.2 Hz (blue). Respiratory oscillations induce immediate vascular pressure oscillations at 180° (1), with a decrease in blood pressure occurring during inspiration and an increase in blood pressure during expiration (Traube-Hering waves, green). Due to the baroreflex, heart rate oscillates immediately with blood pressure changes at a 180° phase relationship (2, green-hatched) and therefore oscillates synchronously with breathing at a 0° phase relationship. On the other hand, heart rate also oscillates in phase (0°) with respiration, but with a delay (blue-hatched, 3), because of the direct influence of respiratory neurons on the vagus nerve. Thus, combined cardiac oscillations (3) are in phase but delayed. The resulting cardiac oscillations (4) are low and irregular, and reflect a low vagally-mediated HRV because the decrease in heart rate during the increase in blood pressure lasts less than 1 sec per cycle (grey box).

During SPB (B), respiration flow oscillates approximately at 0.1 Hz (resonant frequency), and induces mirrored blood pressure oscillations (1) and cardiac oscillations (2). The principal change at this breathing rate is that there is no delay

between respiratory and cardiac oscillations (coherent phases), so combined cardiac oscillations induced by both blood pressure and respiratory changes are in phase and synchronous (3). The resulting cardiac oscillations (4) are high and regular, correspond to a high vagally-mediated HRV because the decrease in heart rate during each increase in blood pressure lasts five seconds per cycle (ideal time for ACh release and hydrolysis).

Baroreflex resonant oscillations are not shown to enhance the clarity of the figure.

Figure 4. Neuronal pathways leading to changes in heart rate during a breathing cycle

During inspiration, cardiorespiratory neurons in the lower medulla activate sympathetic cells. At the same time, changes in intra-thoracic pressure indirectly result in stretch thoracic and atrial receptor activation, and baroreceptor silencing. These pathways contribute to an increase in heart rate. On the contrary, expiration activates parasympathetic neurons, stretch receptors are not activated anymore, and baroreceptors are stimulated: these mechanisms lead to a decrease in heart rate.

Figure 5. Baroreflex resonant oscillations during the SPB

During the SPB (0.1 Hz), baroreflex resonant oscillations are overcome by periodic increases and decreases in heart rate during inspiration and expiration, respectively.

Figure 6: Theoretical model of neurovisceral integration to explain peripheral and central benefits of slow breathing.

During spontaneous breathing (approximately 0.2 Hz), resultant cardiac variations (red oscillations) are small and short-lasting (one second at the most for each expiration) because direct (blue arrow) and indirect (green arrow, baroreflex)

respiratory-induced influences are not synchronous between them and with the resonant frequency (0.1 Hz). Consequently, the duration of acetylcholine (ACh) release and hydrolysis during each expiration is low, and the vagally-mediated HRV (vmHRV) is low. Also, because blood pressure oscillations are small and rapid, vagal inputs to the left prefrontal and limbic regions are weak (small green arrow).

During slow breathing at 0.1 Hz, resultant cardiac variations (red oscillations) are large and long-lasting (5-sec during each expiration) because direct (large blue arrow) and indirect (large green arrow, baroreflex) respiratory-induced influences are synchronous with the resonant frequency. Consequently, the duration of ACh release and hydrolysis during each expiration is high. The level of oxygen delivery during each inspiration is maximal, vmHRV is high and is at the origin of diverse peripheral benefits, including anti-inflammatory and anti-hypertensive effects. Also, the conjunction of high cardiac oscillations and long-lasting blood pressure oscillations increases the activation of interoceptive and limbic structures. These mechanisms may be at the origin of central benefits (Smith et al., 2017).

Amyg: amygdala; Cing: cingulate cortex; Hipp: hippocampus

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Declarations of interest

The authors declare no conflict of interest

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Figure 1

1467

Central rhythm generator neurones

Carotid and aortic baroreceptors

Nucleus ambiguus

Nucleus tractus solitarius

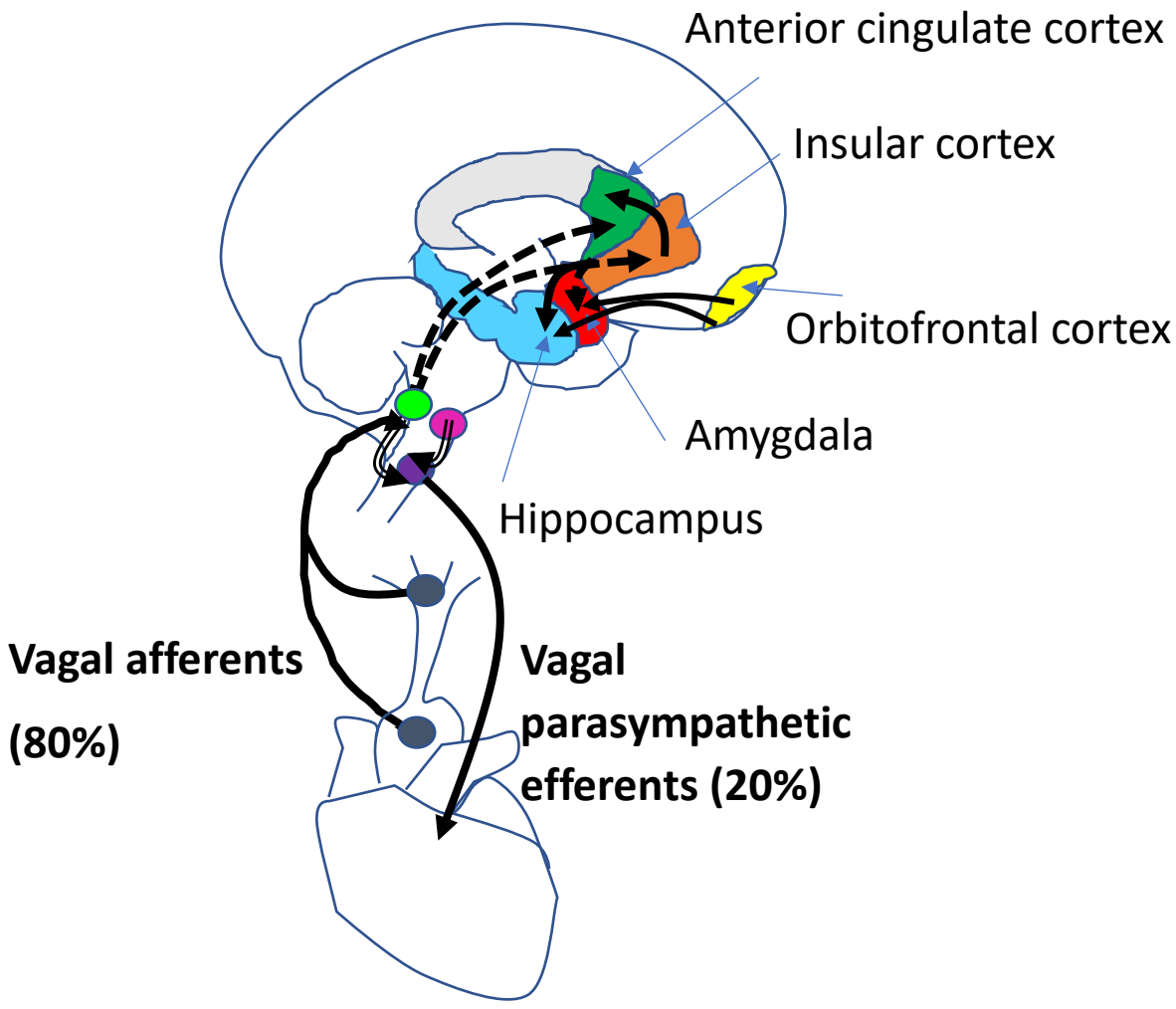

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Figure 2

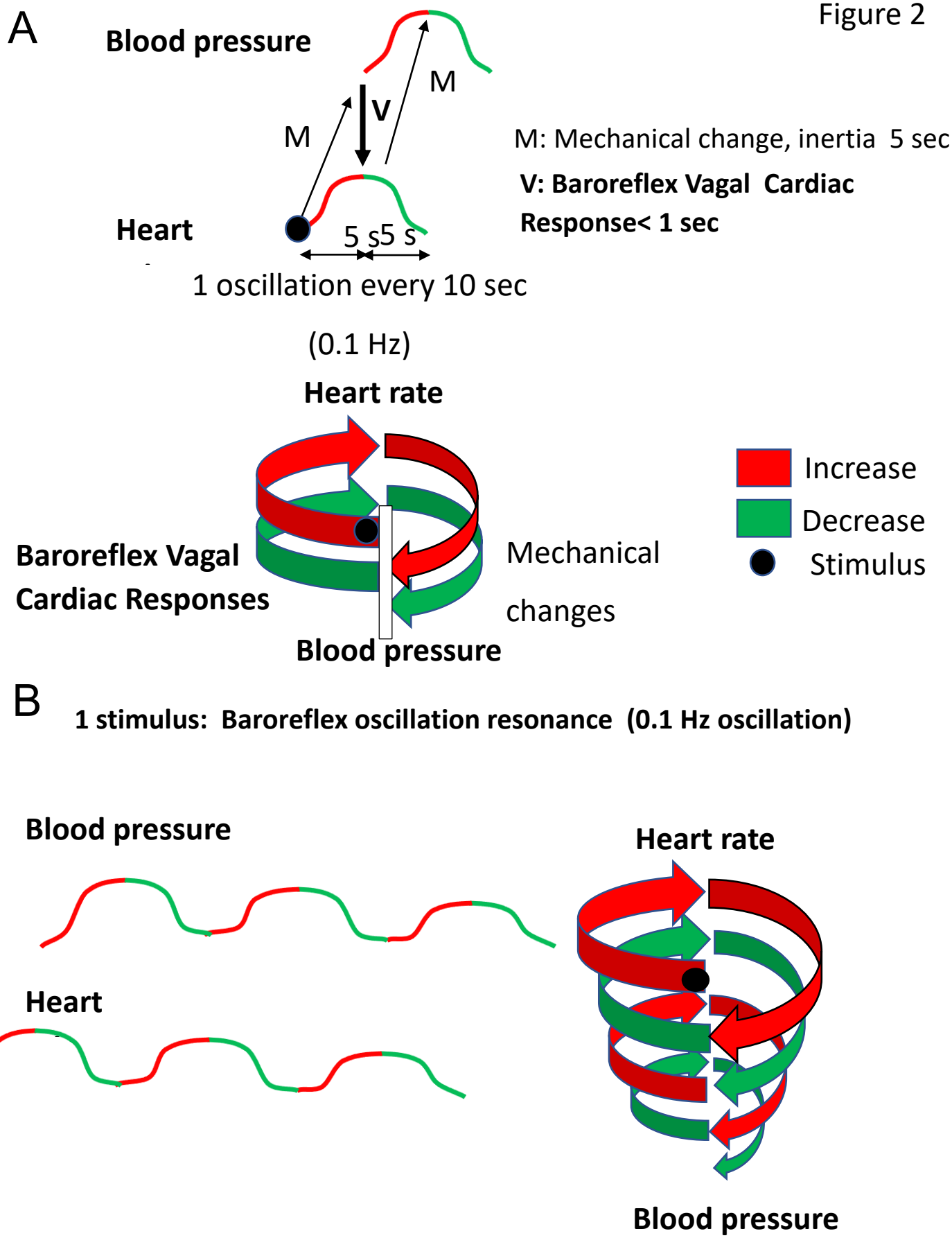
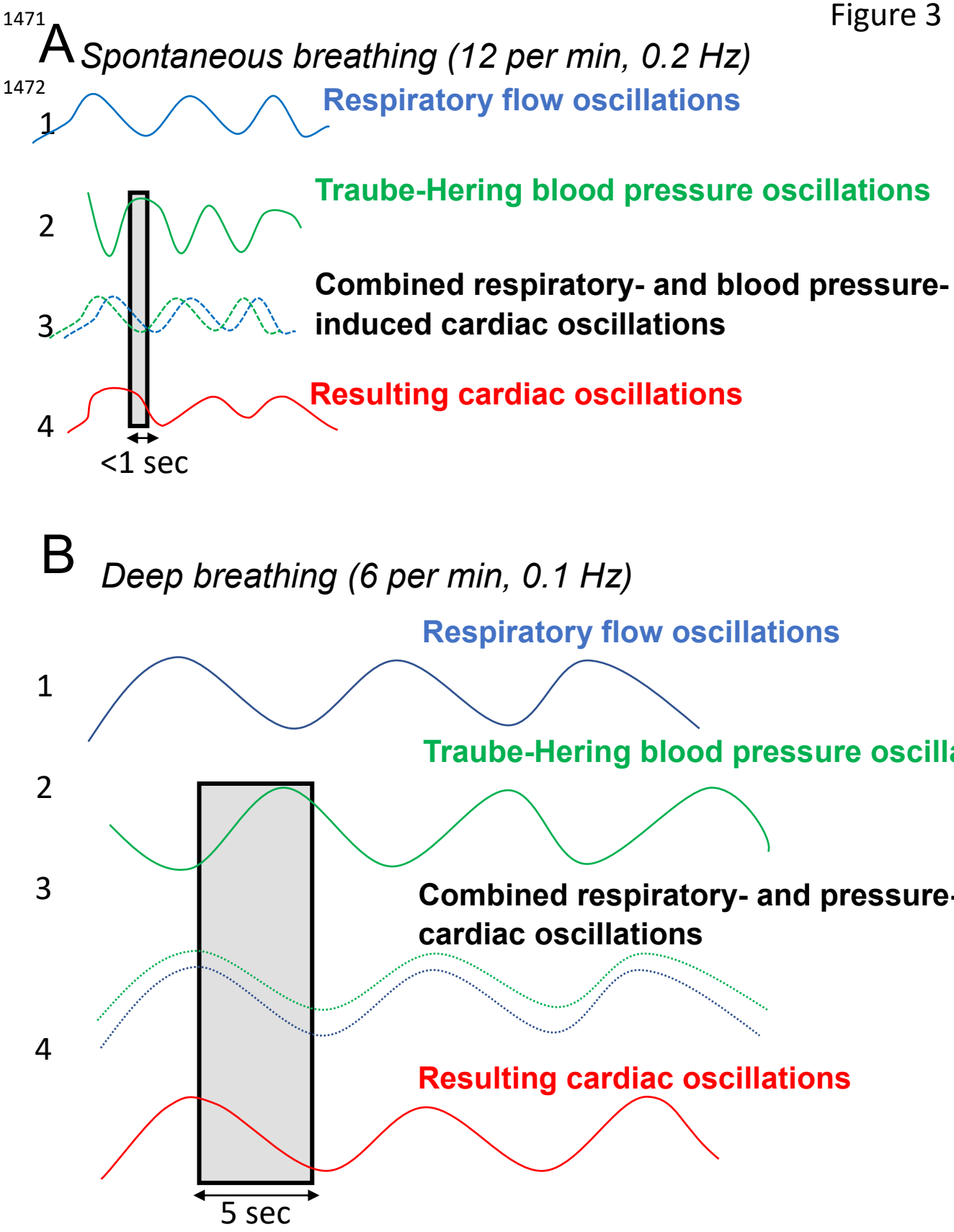


Figure 3


A Spontaneous breathing (12 per min, 0.2 Hz)
Respiratory flow oscillations
Traube-Hering blood pressure oscillations
Combined respiratory- and blood pressure-induced cardiac oscillations
Resulting cardiac oscillations
1
2
3
4
<1 sec
B Deep breathing (6 per min, 0.1 Hz)
Respiratory flow oscillations
Traube-Hering blood pressure oscillations
Combined respiratory- and pressure-induced cardiac oscillations
Resulting cardiac oscillations
1
2
3
4
5 sec

1473

Figure 4

1474

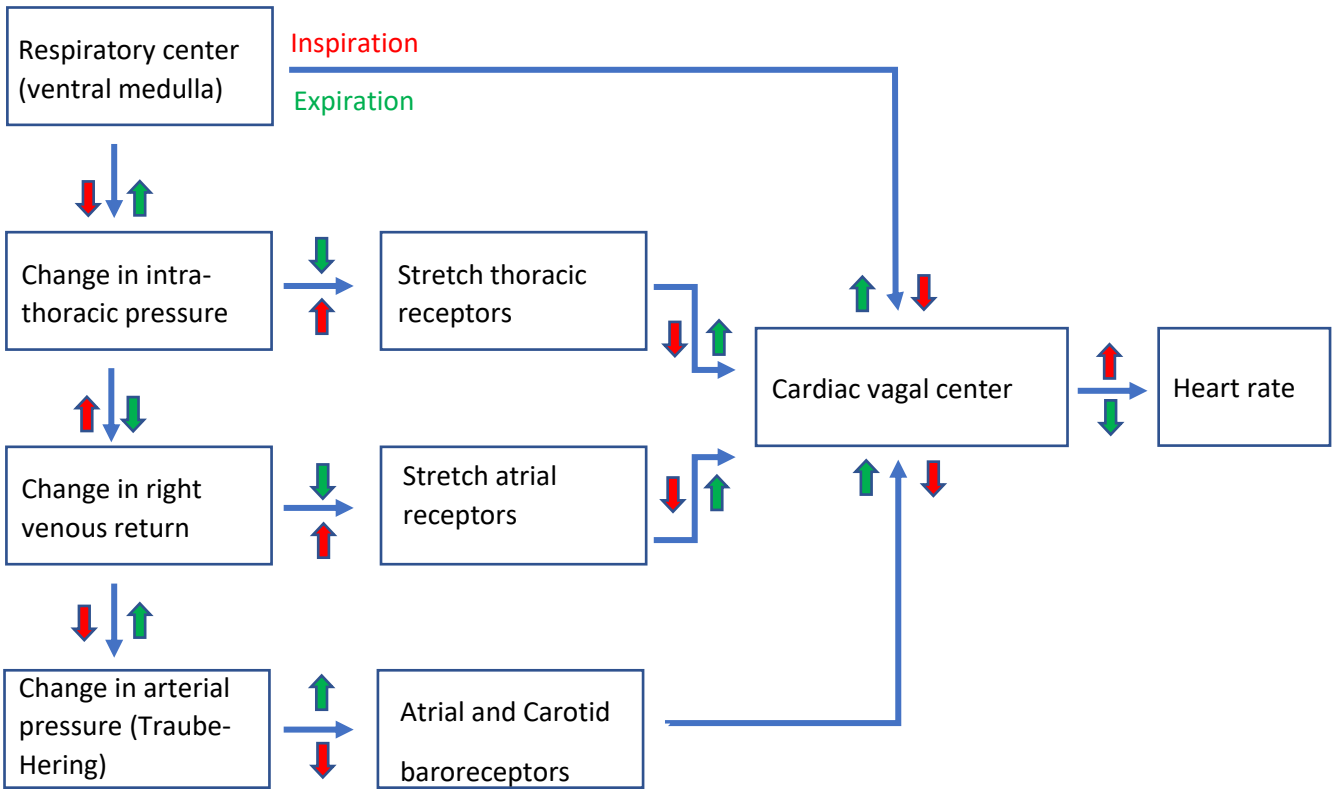


Figure 5

Periodic stimuli (deep breathing, 0.1 Hz): Periodic changes in heart rate

Overcoming baroreflex oscillation resonance

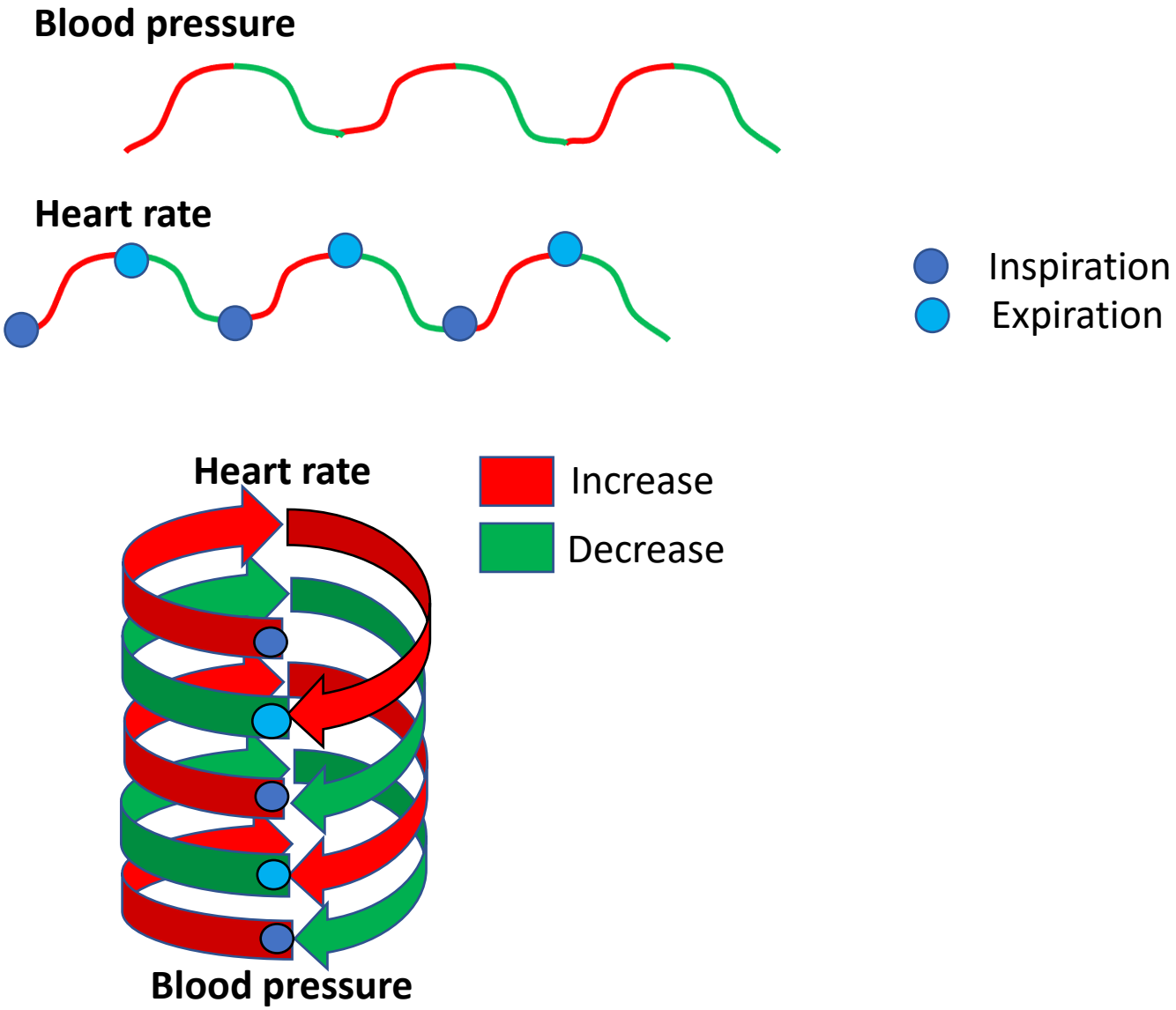
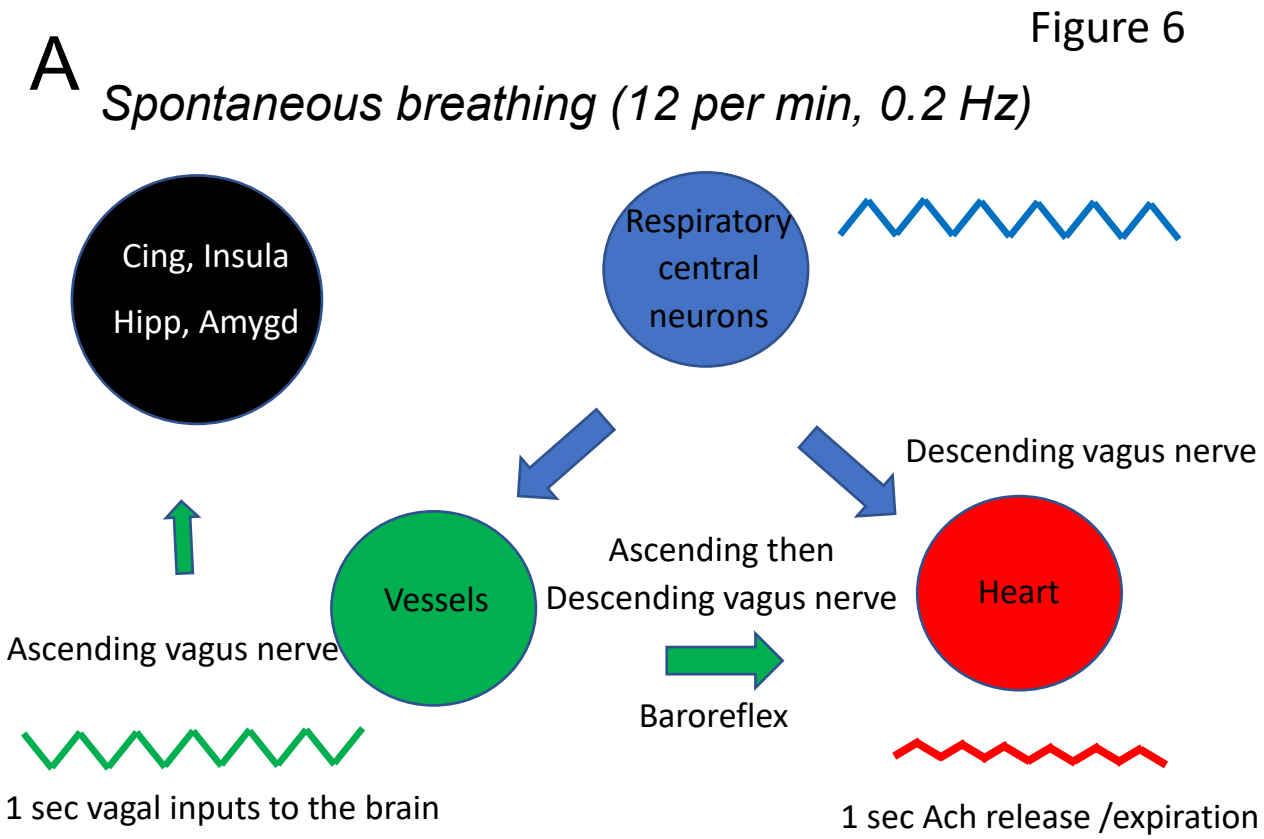
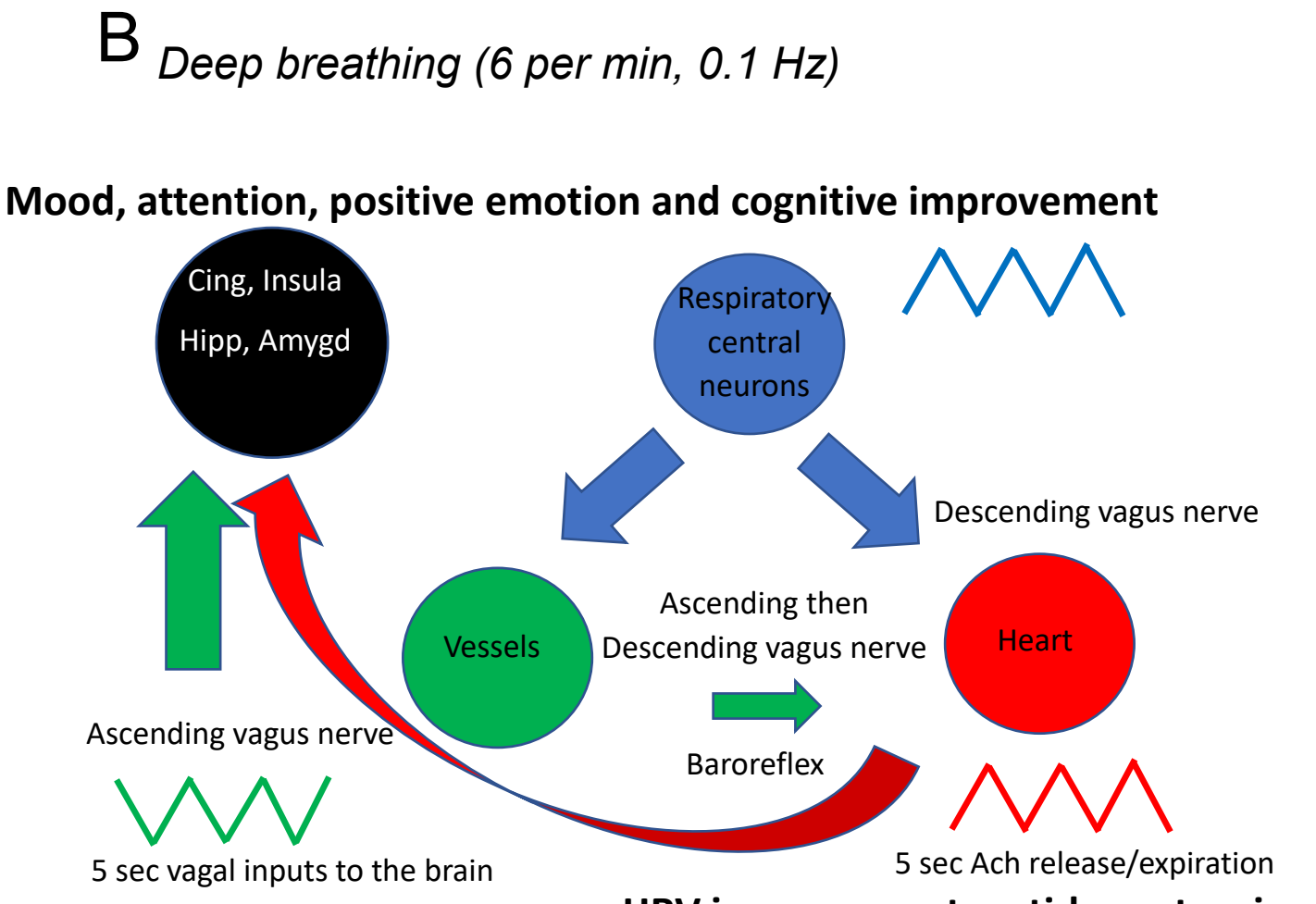


Figure 6


A
Spontaneous breathing (12 per min, 0.2 Hz)
Cing, Insula
Hipp, Amygd
Respiratory central neurons
Descending vagus nerve
Ascending then Descending vagus nerve
Vessels
Heart
Ascending vagus nerve
Baroreflex
1 sec vagal inputs to the brain
1 sec Ach release /expiration


B
Deep breathing (6 per min, 0.1 Hz)
Mood, attention, positive emotion and cognitive improvement
Cing, Insula
Hipp, Amygd
Respiratory central neurons
Descending vagus nerve
Ascending then Descending vagus nerve
Vessels
Heart
Ascending vagus nerve
Baroreflex
5 sec vagal inputs to the brain
5 sec Ach release/expiration
vmHRV improvement, anti-hypertension and anti-inflammation