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1 Heart rate variability and slow-paced breathing:

2 when coherence meets resonance

3

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19 Highlights

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

32

33

34 Abstract

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

50

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

53 I- Introduction

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

72 II- Central and reflex interactions involved in heart rate variability

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

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

82 Over the past few decades, following the publication of HRV guidelines by the Task
83 Force in 1996 (Task Force 1996), the importance of vagally-mediated HRV (vmHRV)
84 has steadily increased (Kleiger et al., 2005; Laborde et al., 2017). In separate
85 proportional hazards regression analyses that adjusted for relevant risk factors, a
86 higher vmHRV was found to be associated with higher life expectancy (Piccirillo et al.,
87 2001, 1998). In addition, greater cognitive flexibility (Colzato et al., 2018), resilience to
88 stress (Hirten et al., 2020), or resistance to temptation in dietary challenges (Maier
89 and Hare, 2017), were also observed in patients with higher vmHRV. These findings
90 illustrate the relevance of vmHRV as a marker positively related to health, wellbeing,
91 and self-regulation.

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

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

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

125 Given the discrepancies noted above, there may be an explanation that might account
126 for some of the heterogeneous findings. It appears that restricting the sympathetic
127 frequency band to 0.05 Hz and 0.1 Hz results in the best sympathetic indicator. While
128 the frequency range of 0.10-0.15 Hz has a significant negative correlation with heart
129 rate, suggesting a stronger parasympathetic influence in this range (Jaffe et al., 1994).
130 A phenomenon called “baroreflex resonance” accounts for the vagal influence in this
131 range, at approximately 0.1 Hz (Kromenacker et al., 2018; Vaschillo et al., 2002,
132 2006), and is described as a “negative feedback” system with a constant delay
133 (Lehrer, 2013). Both heart rate and blood pressure vary in a closed-loop so that a
134 change in either function causes a change in the other. When carotid and aortic
135 baroreceptors are activated following an increase in mean arterial pressure, vagal and
136 glossopharyngeal afferents are stimulated and send inputs to baroreceptor-second
137 order neurons in the nucleus of the tractus solitarius (located in the lower dorsal
138 brainstem) (Housley et al., 1987; Norcliffe-Kaufmann, 2019) (Figure 1). Cardiac vagal
139 motor neurons in the ventral medulla (located mainly in the nucleus ambiguus)
140 (McAllen and Spyer, 1978) are then stimulated and subsequently produce a reflex
141 decrease in heart rate following the release of acetylcholine (ACh) by vagal
142 parasympathetic efferents onto the heart (baroreflex cardiac response) (Fritsch et al.,
143 1991; Guyenet et al., 1987) (Figure 1). This bradycardia buffers the initial increase in
144 blood pressure. On the contrary, a decrease in blood pressure will halt baroreceptor
145 activity, and heart rate will increase. However, heart rate and blood pressure reaction
146 shifts are not instantaneous. For one stimulus that increases heart rate, the resulting
147 increase in blood pressure (due to an increase in the quantity of blood circulating
148 during each cardiac pulse) is delayed by approximately five seconds, because of
149 inertia and plasticity in the blood coursing through the vascular system (Vaschillo et

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

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

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

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

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

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

189 Respiratory-induced pressure oscillations result largely from the mechanical
190 interaction between respiration and cardiac output (Figure 4) (Montano et al., 2000).
191 During each inspiration and increase in negative intrathoracic pressure, a rapid
192 increase in venous return in the right ventricle associated with a decrease in cardiac
193 output occurs, leading to an associated decrease in arterial pressure (Verhoeff and
194 Mitchell, 2017). These oscillations, called Traube-Hering waves, are “out of phase”
195 (180°) with the respiratory flow (Billman, 2011). Because of the tonic activation of the
196 baroreflex (see above), vagal cardiac oscillations immediately compensate for these
197 vascular pressure changes. The resulting cardiac oscillations are at 180° with blood
198 pressure oscillations and thus “in phase” (0°) with respiratory changes (Figure 3A). To

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

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

210 Vagally-mediated RSA can be modulated by superior central influences through their
211 actions on vagal motor neurons. For example, direct and indirect influences of central
212 structures involved in stress, like the dorsomedial nucleus of the hypothalamus
213 (DiMicco et al., 2002; Sévoz-Couche et al., 2013, 2003; Sévoz-Couche and Brouillard,
214 2017), decrease the baroreflex gain and reduce the tonic baroreceptor drive on vagal
215 motor neurons. This results in the diminution of the basal level of vagal activity and
216 therefore the decrease of RSA (Brouillard et al., 2020, 2019; Sévoz-Couche et al.,
217 2013, 2003). In addition, stress increases sympathetic activity that has a negative
218 influence on parasympathetic tone because RSA is slightly enhanced by atenolol or
219 propranolol, two beta-adrenergic receptor blockers in humans (Pagani et al., 1986;
220 Pomeranz et al., 1985; Taylor et al., 2001), though this result could not be reproduced
221 in rats (Pereira-Junior et al., 2010). To note, RSA is not only affected in diseases linked
222 to stress but also in pathological conditions with vagal inhibition like Parkinson's

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

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

230 III- SPB & RSA

231 Breathing is suggested to be the origin of RSA; therefore, RSA amplitude is
232 modified by respiratory frequency. An increase in respiratory frequency leads to a
233 progressive decline in RSA as vagal effectors become less able to follow higher
234 frequency variations (Berger et al., 1989). On the contrary, a reduction in the breathing
235 rate can increase RSA. To avoid hypoventilation and maintain minute ventilation (VE),
236 tidal volume (Vt) must increase when respiratory frequency (f) decreases, **given that**
237 $VE=Vt*f$. Hence, SPB is usually associated with deep (but not forced) changes in
238 thoracic volume. When **the** breathing rate is below 0.15 Hz, RSA is found in the low-
239 frequency domain (Kromenacker et al., 2018). Kromenacker and colleagues (2018)
240 showed that HRV power across the low-frequency range was found to be nearly
241 eliminated by the parasympathetic blockade during SPB, while similar spectral power
242 during sympathetic blockade and placebo was statistically indistinguishable,
243 reinforcing the fact that RSA is vagally-mediated even during SPB.

244 *Effects of SPB on RSA and cardiac oscillation amplitude*

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

247 until a plateau was reached at approximately 0.1 Hz (6 cpm) (Hirsch and Bishop,
248 1981). They also observed that RSA is influenced by respiratory volume (RSA at 0.1
249 Hz was higher for a tidal volume of 3 l than for 0.5 l). However, after RSA normalization
250 for tidal volume, they found that normalized points fell within two-SD of the 1 l curve
251 and concluded that the system behaved as a linear function over the entire frequency
252 range from 0.4 to 0.1 Hz, but not below. Accordingly, an increase in total HRV
253 (including RSA amplitude) was observed during SPB (6 cpm) compared with
254 spontaneous breathing (between 0.1 and 0.2 Hz) and paced breathing at 0.2 Hz (Tsai
255 et al., 2015). RSA amplitude depends on the variation in cardiac oscillations. The
256 calculation of maximal cardiac (deltaHR) changes during acute SPB seems to be more
257 sensitive to indicate an increase in cardiac vagal activity than the usual HRV analyses
258 (e.g., RMSSD) (Löllgen et al., 2009) or classic autonomic tests (Izzi et al., 2018).

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

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

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

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

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

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

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

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

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

335 A fourth explanation may also account for the improvement of vagal activity
336 during SPB. Central respiratory generators are modulated by lung stretch **receptor**
337 activation during large inspiration to inhibit medullary inspiratory neurons and start
338 expiration (Loewy and Spyer, 1990; Moreira et al., 2007), and this phenomenon may
339 influence RSA amplitude. Recently, Noble and Hochman (2019) suggested that there
340 was a preferential recruitment of slowly-adapting pulmonary afferents during
341 prolonged inhalation, as in slow-paced and deep breathing, to improve exhalation
342 (Noble and Hochman, 2019). However, direct central neural mechanisms seem
343 crucial, as no RSA can be observed in a transplanted heart until autonomic
344 reinnervation (Sands et al., 1989). Intra-cellular recordings of vagal motor neurons
345 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

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

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

378 IV- Slow-paced Deep Breathing positive effects

379 1- Peripheral benefits

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

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

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

394 cases (Miller et al., 2006). In the same manner, we and others found that an animal
395 model of psychosocial stress leads to a vulnerability to persistent autonomic
396 dysfunction, cardiac hypertrophy, and ventricular ectopic beats, but only in the group
397 of animals associated with persistent low vagal temporal and frequential parameters
398 in HRV (Brouillard et al., 2020; Sgoifo et al., 1998). More specifically, a
399 parasympathetic recovery in resilient animals is a sign of protection against cardiac
400 events (Brouillard et al., 2020). This supports the potential beneficial effects of SPB
401 on cardiac events during stress episodes, with a better balance in autonomic
402 innervation. According to this hypothesis, a study reported a beneficial effect of a daily
403 practice of SPB (6 cpm) on the frequency of premature ventricular complexes (PVC)
404 in Indian women, though only in five of a series of 10 consecutive patients with frequent
405 (≥ 10 /minutes) unifocal PVC (Prakash et al., 2006). It is also suggested that SPB may
406 be at the origin of ventricular synchrony (Dadu and McPherson, 2013).

407 When examining vascular pressure, systolic blood pressure decreases during acute
408 (a few minutes) SPB practice in healthy participants (Dick et al., 2014) or during
409 chronic (8 weeks) practice in American patients with hypertension (Bertisch et al.,
410 2011). SPB also induces a reduction in blood pressure in healthy lowlanders (from
411 Italy) exposed to acute or prolonged high altitudes (Bilo et al., 2012). However, these
412 studies did not compare slow breathing to other interventions. This comparison is very
413 important to estimate the part of distraction in the beneficial effect of SPB. Actually, in
414 a participant blinded, multi-centre, randomised controlled trial was conducted in which
415 the participants in the intervention group (IG) practiced deep breathing exercises
416 guided by sound cues while those in the control group (CG) listened to the music
417 during 8 weeks, both IG and CG interventions were associated with a clinically
418 significant reduction in blood pressure. Importantly, deep breathing exercises did not

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

427 When examining oxygen saturation **in Malaysian patients**, increases were observed
428 during 5, 7, or 9 minutes of slow-paced deep breathing (Cheng and Lee, 2018).
429 **According to** the same line of argumentation, healthy lowlanders exposed to acute or
430 prolonged high altitude had an increase in ventilation efficiency during deep breathing,
431 as shown by the significant increase in blood oxygen saturation (reduction in the
432 alveolar arterial PO₂ difference consistent with improvements in ventilation-perfusion
433 mismatch), and **reduced** dead space minute ventilation during SPB (Bilo et al., 2012).
434 This is consistent with animal experiments **that** reported a model simulating RSA that
435 gas exchange at the alveoli is most efficient when heart rate starts increasing at the
436 beginning of inhalation and starts decreasing just as exhalation starts, i.e., at an exact
437 0° phase relationship (Hayano et al., 1996). It is noteworthy that nose breathing alone
438 also imposes approximately 50 percent more resistance to the air stream, as
439 compared to mouth breathing (Cottle, 1958). This results in 10 to 20 percent more
440 oxygen uptake. Nasal breathing, as opposed to mouth breathing, increases circulating
441 blood oxygen and carbon dioxide levels, and improves overall lung volumes.

442 *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-

468 6 but not TNF- α (inflammatory markers) (Leelarungrayub et al., 2018). In another study
469 lasting three months, using device-guided SPB for a respiration rate of 6 cpm, a
470 significant continuous decrease in mean blood pressure associated with reduced
471 levels of blood pro-inflammatory cytokines (including TNF- α) was found in patients
472 from Taiwan suffering from hypertension (Wang et al., 2021). The findings suggest
473 that SPB realized exactly at 6 cpm may have a stronger effect on inflammation than a
474 non-controlled reduction in breathing rate. This hypothesis should be interpreted with
475 caution, as another study found no effect of HRV-BF on inflammation. The HRV-BF
476 group showed significant attenuation of the LPS-induced decline in HRV for the 6
477 hours following LPS exposure. HRV-BF also reduced symptoms of headache and eye
478 sensitivity to light following lipopolysaccharide (LPS) exposure, but did not affect LPS-
479 induced levels of pro-inflammatory cytokines or symptoms of nausea, muscle aches,
480 or feverishness (Lehrer et al., 2010).

481 The mechanism involved in the potential anti-inflammatory effect of SPB may involve
482 vagal stimulation. This has been extensively described in Tracey et al. (2002). Besides
483 humoral and cellular regulation, neural regulation is required for the host to fight
484 against pathogens and resolve inflammation (Tracey, 2002). Electrical stimulation of
485 the vagus nerve can trigger the synthesis of ACh in the spleen. Splenic macrophages
486 express $\alpha 7$ nicotinic ACh receptors, which are activated by ACh to suppress the
487 activation of pro-inflammatory cytokines (Reid, 2008; Smith and Reid, 2006), and this
488 modulatory mechanism is termed the Cholinergic Anti-inflammatory Pathway (CAP).
489 Vagus nerve endings are also reported to innervate the distal airways of the lung, even
490 in the alveoli (Fox et al., 1980; Hertweck and Hung, 1980), explaining the possible
491 mechanisms of SPB's influence on inflammation in respiratory diseases as discussed
492 above.

493

2- Central benefits

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

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

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

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

529 ***NeuroPhysiological effects of SPB:***

530 *Modifications in functional magnetic resonance imaging (fMRI)*

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

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

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

560 *Modification in EEG frequency bands*

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

565 mean power of the alpha and beta bands - involved in anxiety control (Mennella et al.,
566 2017; Pavlenko et al., 2009) - **was** reduced compared with the control group, even at
567 a **seven-day** follow-up (Cheng et al., 2018). It is important to note that **respiration** itself,
568 via sensory inputs from the olfactory bulb, modulates neuronal oscillations in the delta
569 and gamma frequency bands in the neocortex of awake mice (Ito et al., 2014), and
570 respiration through the nose but not the mouth synchronizes electrical activity in the
571 human piriform (olfactory) cortex, as well as in limbic-related brain areas, including **the**
572 amygdala and hippocampus (Zelano et al., 2016).

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

577 ***Neuropsychological effects of SPB***

578 *Pain sensation regulation*

579 Several studies suggest a link between SPB and pain ratings. When practiced acutely
580 (2 min) (Chalaye et al., 2009) or chronically (4 weeks) in US veterans suffering from
581 chronic back pain (Berry et al., 2014), both SPB and HRV-BF were effective in
582 reducing perceived pain. Similar results were found in both American men and women
583 with fibromyalgia syndrome (Reneau, 2020; Zautra et al., 2010), respectively. To note,
584 the study by Reneau showed that the patients who completed the entire experiment
585 with HRV-BF realized 20-minutes daily instead of the 20-minutes twice daily initially
586 planned. These results may suggest that the duration **of** chronic SPB practice should
587 not exceed 20 minutes to ensure better compliance. **When** comparing the effects of
588 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

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

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

626 *Interoception: awareness, decision-making, and concentration*

627 An increase in activity in left insular and cingulate regions during vagal stimulation (see
628 above) suggests that interoceptive awareness and accuracy may be obtained during
629 SPB. However, mixed results have been found on this matter. When a heartbeat
630 discrimination task was presented before and after 20-minutes of either HRV-BF, SPB,
631 or a control condition (viewing a film clip), a general tendency for improvement in
632 heartbeat detection accuracy was reported across all intervention groups of German
633 participants, but groups did not differ significantly (Rominger et al., 2021). These data
634 suggest that distraction, more than a reduced breathing rate, may improve
635 interoception accuracy. On the other hand, RSA and BRS during SPB (5 minutes)
636 were found to positively correlate with increases in interoceptive accuracy (recognition
637 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

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

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

683 *Addiction*

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

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

769 **Figures captions**

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

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

789 **Figure 2: “Baroreflex Resonance” at 0.1 Hz**

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

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

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

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

802 A- During spontaneous breathing, respiration flow oscillates at approximately 0.2 Hz
803 (blue). Respiratory oscillations induce immediate vascular pressure oscillations at
804 180° (1), with a decrease in blood pressure **occurring during inspiration and an**
805 **increase in blood pressure during expiration** (Traube-Hering waves, green). Due to the
806 baroreflex, heart rate oscillates immediately with blood pressure changes at a 180°
807 phase relationship (2, green-hatched) and therefore oscillates synchronously with
808 breathing at a 0° phase relationship. On the other hand, heart rate also oscillates in
809 phase (0°) with respiration, but with a delay (blue-hatched, 3), because of the direct
810 influence of respiratory neurons on the vagus nerve. Thus, combined cardiac
811 oscillations (3) are in phase but delayed. The resulting cardiac oscillations (4) are low
812 and irregular, and reflect a low vagally-mediated HRV because the decrease in heart
813 rate during the increase in blood pressure lasts less than 1 sec per cycle (grey box).

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

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

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

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

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

832 **Figure 5. Baroreflex resonant oscillations during the SPB**

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

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

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

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

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

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

856

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860 **Declarations of interest**

861 The authors declare no conflict of interest

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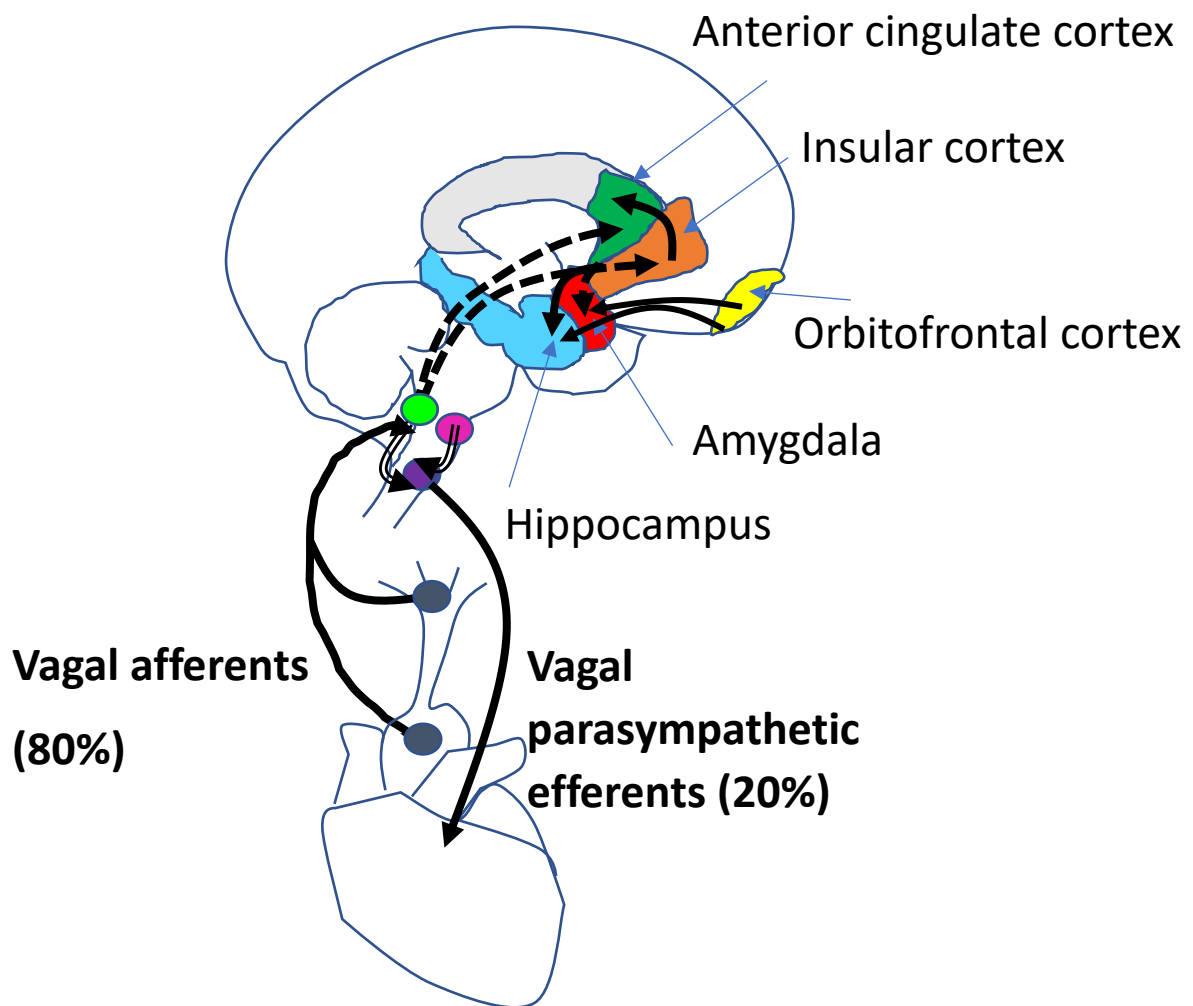
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Figure 1

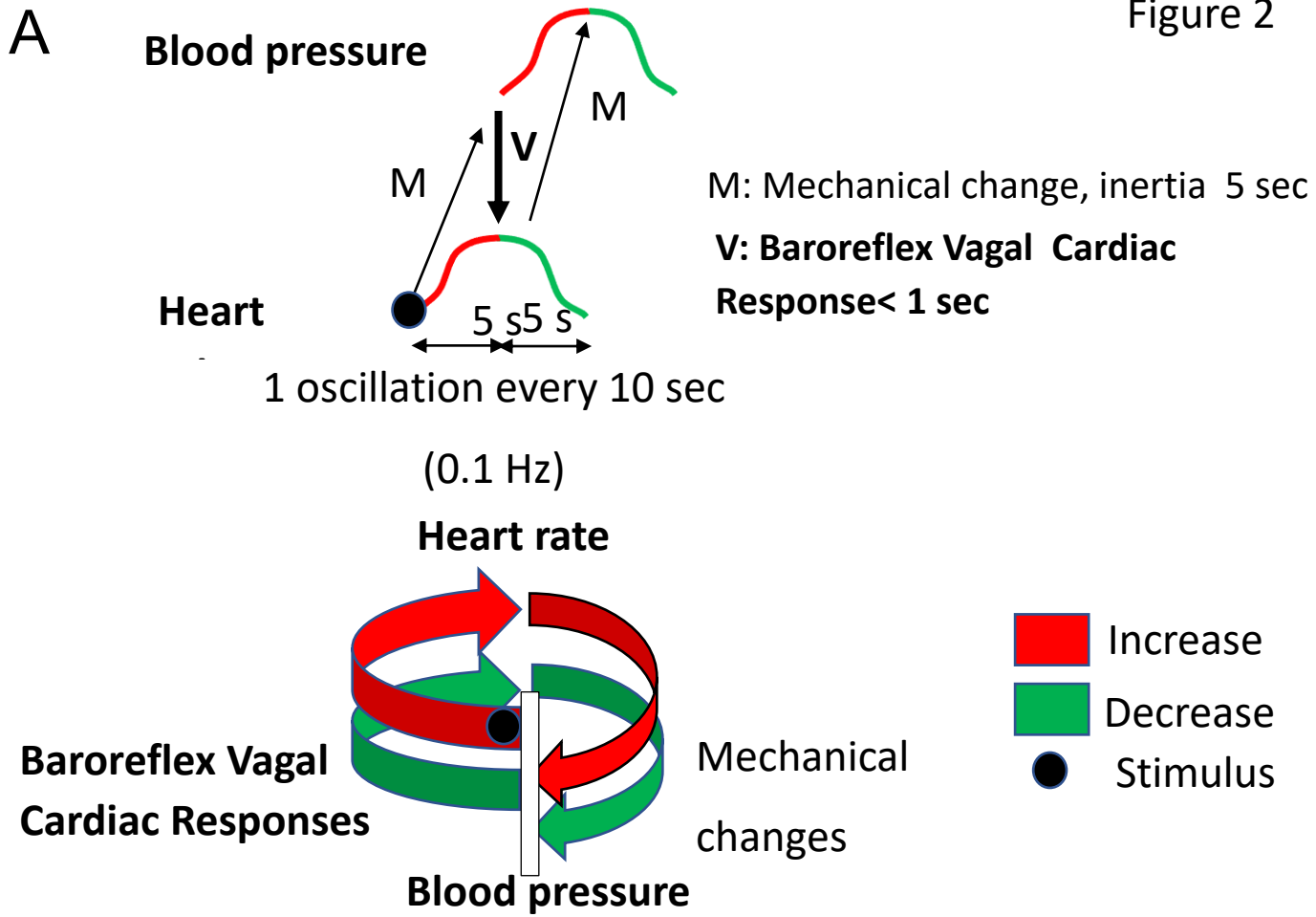
1467

- Central rhythm generator neurones
- Carotid and aortic baroreceptors
- Nucleus ambiguus
- Nucleus tractus solitarius



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Figure 2



B 1 stimulus: Baroreflex oscillation resonance (0.1 Hz oscillation)

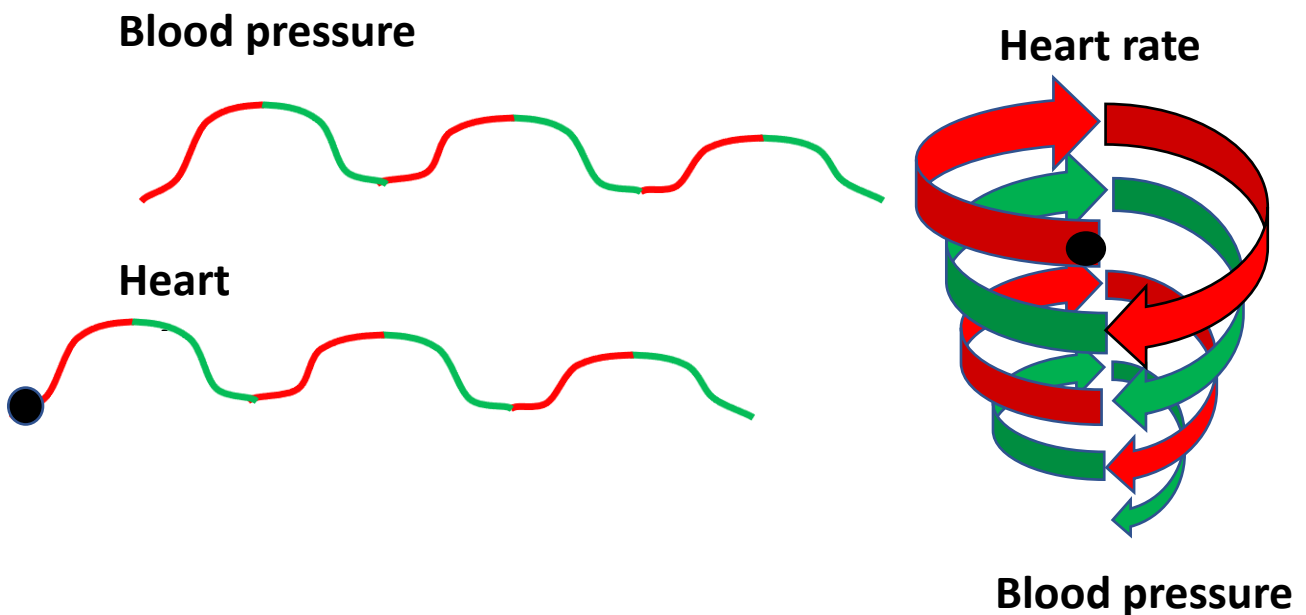
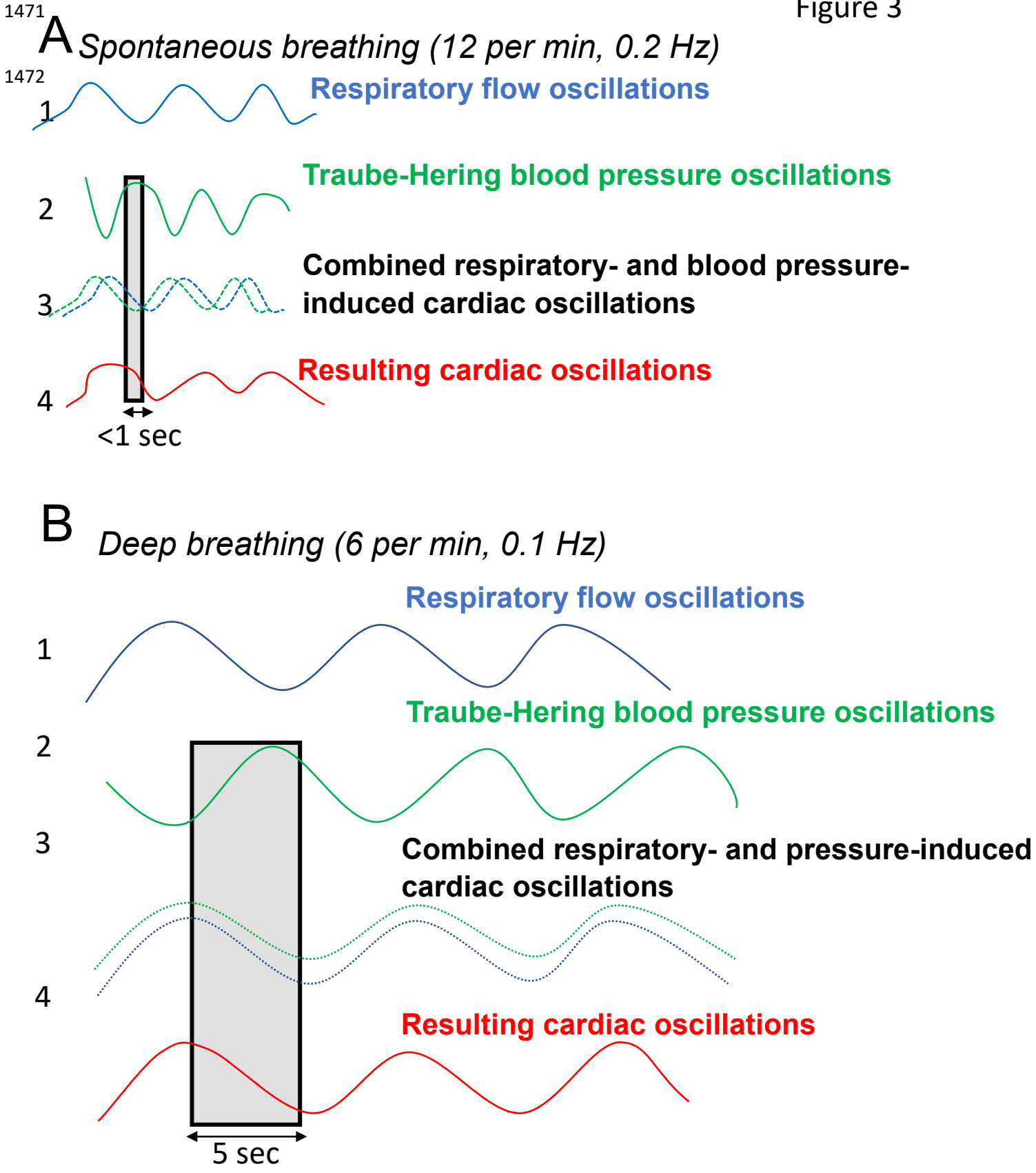


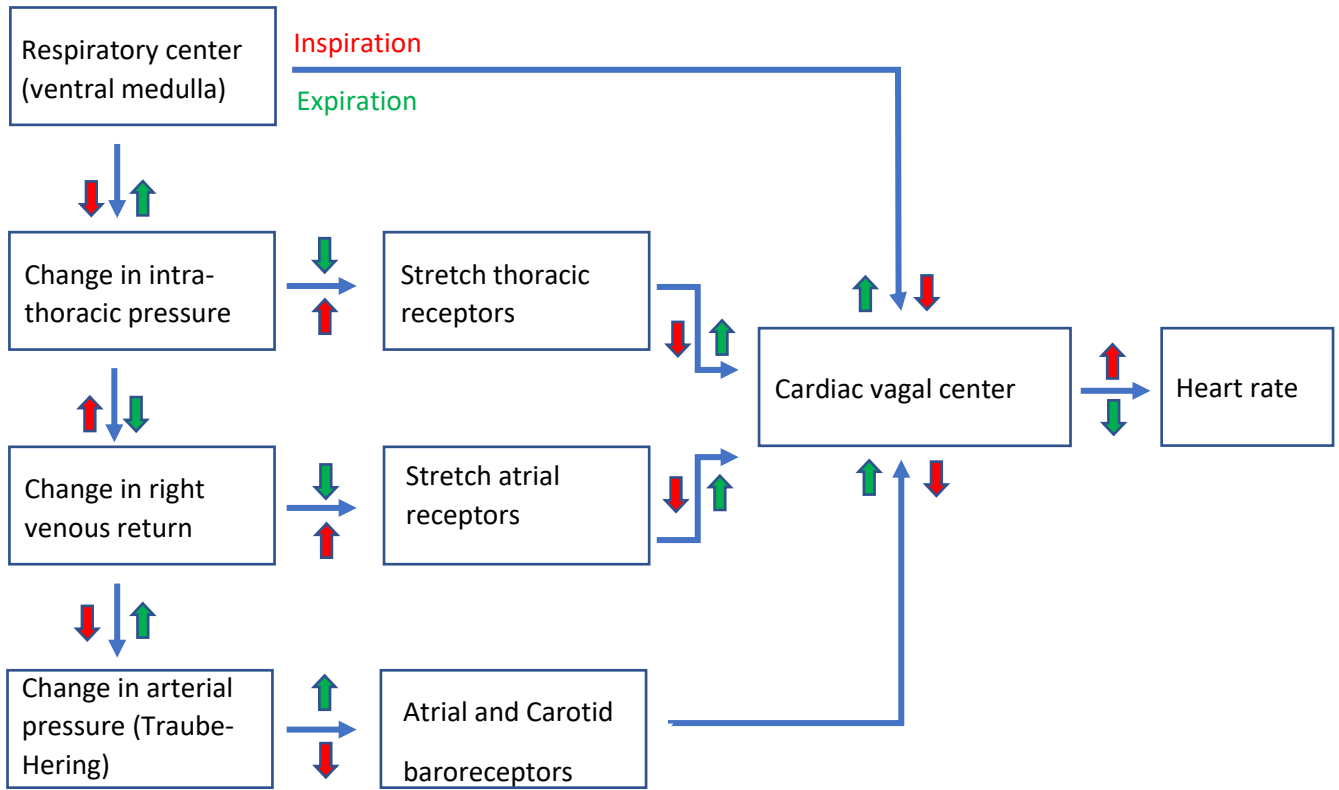
Figure 3



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Figure 4

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1475 **Periodic stimuli (deep breathing, 0.1 Hz): Periodic changes in heart rate**
Overcoming baroreflex oscillation resonance

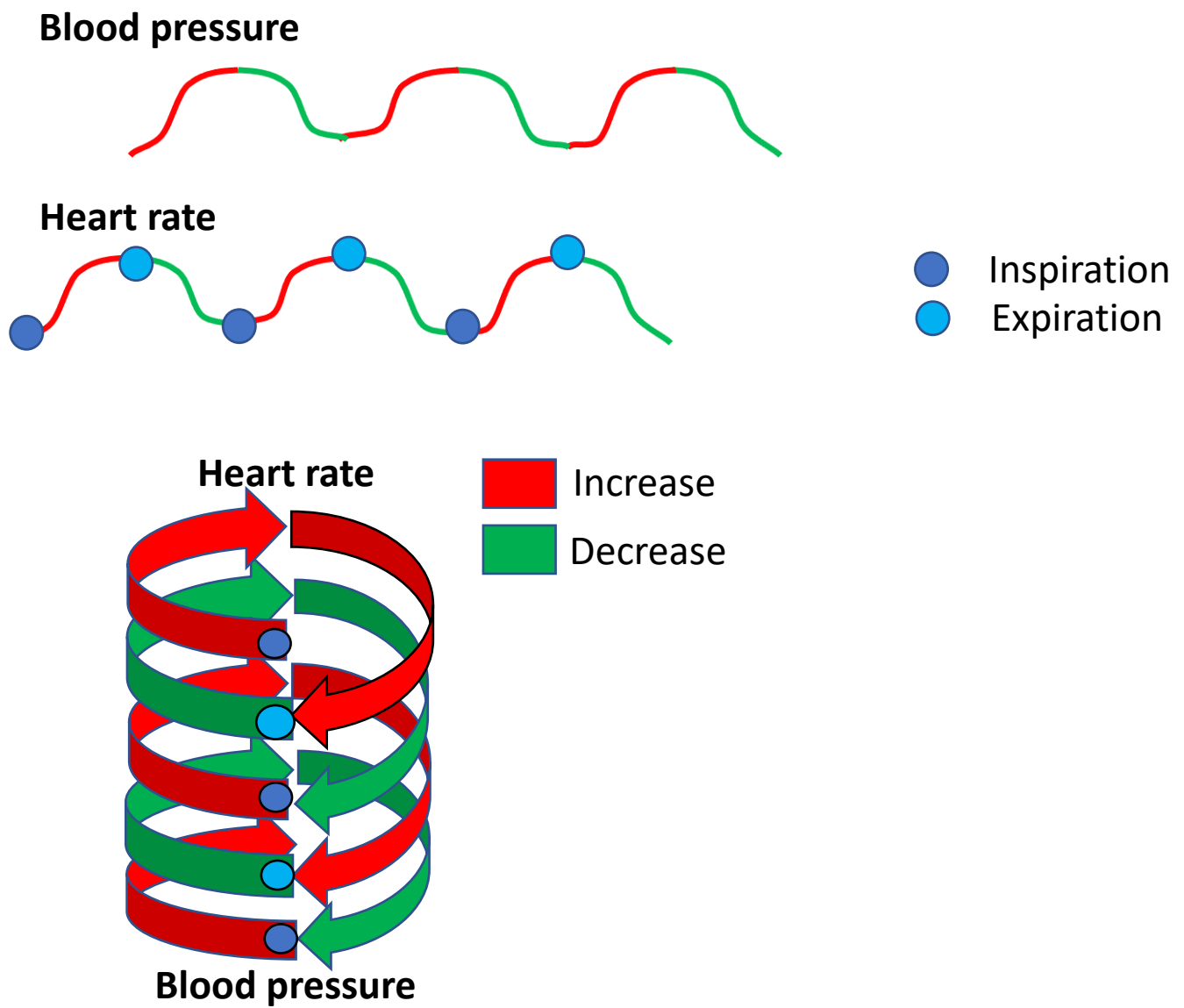


Figure 6

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A *Spontaneous breathing (12 per min, 0.2 Hz)*

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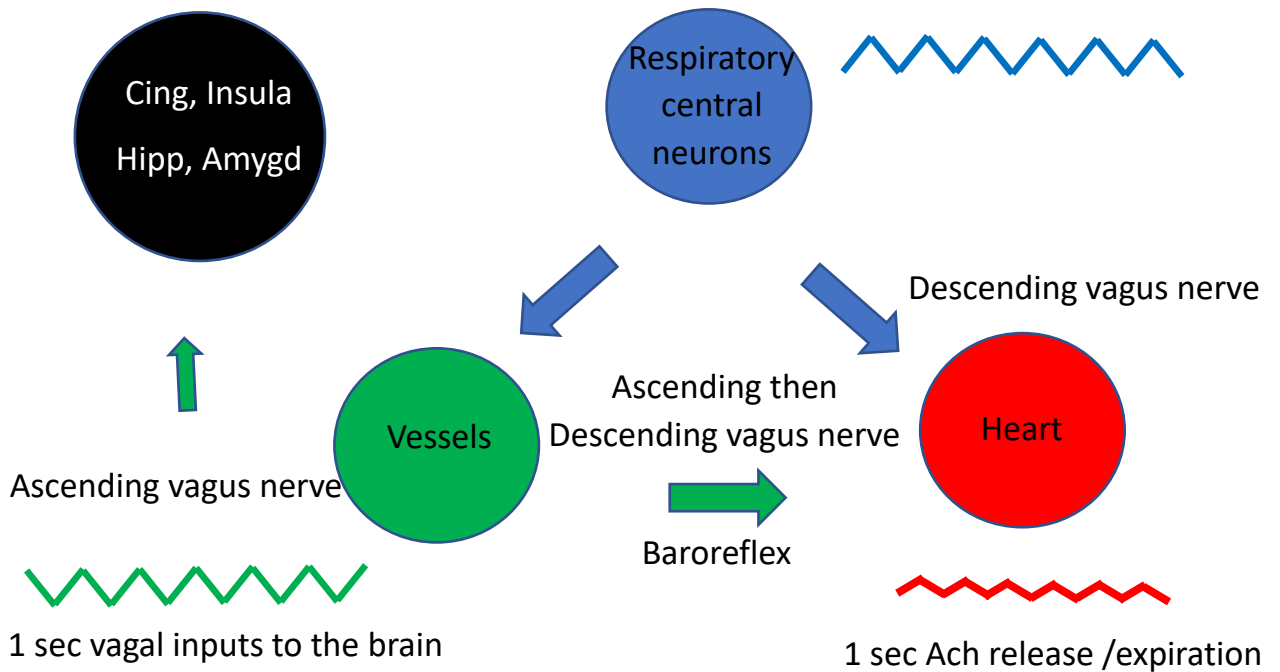
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B *Deep breathing (6 per min, 0.1 Hz)*

Mood, attention, positive emotion and cognitive improvement

