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FROM PSYCHOLOGICAL MOMENTS TO MORTALITY: A MULTIDISCIPLINARY SYNTHESIS ON HEART RATE VARIABILITY SPANNING THE CONTINUUM OF TIME

Andrew H. Kemp^{a,b,*}

Julian Koenig^c

Julian F. Thayer^d

^aDepartment of Psychology, Swansea University, Swansea, United Kingdom

^bDiscipline of Psychiatry, and School of Psychology, University of Sydney, Sydney, Australia

^cSection for Translational Psychobiology in Child and Adolescent Psychiatry, Department of Child
and Adolescent Psychiatry, Centre for Psychosocial Medicine, University of Heidelberg,
Heidelberg, Germany

^dDepartment of Psychology, The Ohio State University, 1835 Neil Avenue, Columbus, Ohio, 43210,
USA

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27***Corresponding author:** Dr Andrew H. Kemp, Department of Psychology, College of Human and
28Health Sciences, Swansea University, Vivian Tower, Singleton Park, SWANSEA SA2 8PP; Tel.:
29+44 (0) 1792 604561. E-mail address: A.H.Kemp@swansea.ac.uk or andrew.kemp@sydney.edu.au
30(Andrew H. Kemp).

31

Abstract

32Heart rate variability (HRV) indexes functioning of the vagus nerve, arguably the most important
33nerve in the human body. The Neurovisceral Integration Model has provided a *structural*
34*framework* for understanding brain-body integration, highlighting the role of the vagus in adaptation
35to the environment. In the present paper, we emphasise a *temporal framework* in which HRV may
36be considered a missing, structural link between psychological moments and mortality, a proposal
37we label as Neurovisceral Integration Across a Continuum of Time (or NIACT). This new
38framework places neurovisceral integration on a dimension of time, highlighting implications for
39lifespan development and healthy aging, and helping to bridge the gap between clearly demarcated
40disciplines such as psychology and epidemiology. The NIACT provides a novel framework, which
41conceptualizes how everyday psychological moments both affect and are affected by the vagus in
42ways that have long-term effects on mortality risk. We further emphasize that a longitudinal
43approach to understanding change in vagal function over time may yield novel scientific insights
44and important public health outcomes.

45

46**Keywords:** health psychology, psychiatry, epidemiology, public health, psychophysiology,
47autonomic nervous system, heart rate variability, psychophysiological rigidity, psychophysiological
48flexibility, resilience, emotion, mood, mood disorders, cytokines, inflammation, biomarkers,
49atherosclerosis, cardiovascular disease, morbidity, mortality, polyvagal theory, neurovisceral
50integration model, research domain criteria, mental health, physical health

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Introduction

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90“An oak and a reed were arguing about their strength. When a strong wind came up, the reed
91avoided being uprooted by bending and leaning with the gusts of wind. But the oak stood firm and
92was torn up by the roots.” — Aesop (620BC – 560 BC)

93

94The 1990’s was designated as ‘the decade of the brain’ and, more recently, Thomas Insel has
95proposed that mental disorders now be considered ‘brain disorders’ (Insel, 2013). Insel’s position is
96that changes in the brain associated with psychiatric illness occur much earlier than observable
97symptoms. Waiting for observable symptoms therefore, leads to delays in appropriate diagnosis and
98treatment, a situation, Insel argues, that is akin to waiting for a myocardial infarction before treating
99the underlying cause. This position has important implications for early detection and early
100intervention. However, it also leads to the perception that the emotions and their disorders are
101divorced from physical health, a perception that could not be farther from the truth, as we will
102demonstrate here. An excellent candidate for providing a critical structural link between
103psychological moments and mortality is heart rate variability (HRV), a proposal we label as
104Neurovisceral Integration Across a Continuum of Time (or NIACT) and describe in the present
105manuscript. HRV refers to the millisecond variation between consecutive heartbeats and reflects the
106pulse of vagal nerve activity on the sinoatrial node. The word “vagus” is Latin for wandering,
107referring to the extensive distribution of the vagus nerve (cranial nerve X) throughout the body.

108

109Research on HRV has focused on a wide range of behaviours including positive mood states (Kok
110& Fredrickson, 2010; Kok et al., 2013; Oveis et al., 2009), emotion regulation (Butler, Wilhelm, &
111Gross, 2006; Di Simplicio et al., 2012; Geisler, Vennewald, Kubiak, & Weber, 2010), cognitive
112function (Hansen, Johnsen, & Thayer, 2003; Hansen, Thayer, Johnsen, Sollers, & Stenvik, 2004;
113Suess, Porges, & PLUDE, 1994), as well as a variety of biological functions including metabolic
114homeostasis (Tracey & Pavlov, 2012), inflammatory processes (Tracey, 2002) and even brain
115plasticity (Hays, Rennaker, & Kilgard, 2013). Alterations in HRV may also underpin a host of
116conditions and diseases including psychiatric illness and cardiovascular disease (Kemp & Quintana,
1172013; Thayer, Yamamoto, & Brosschot, 2010c), while stimulation of the vagal nerve has been used
118as a treatment for refractory epilepsy (Shahwan, Bailey, Maxiner, & Harvey, 2009) and depression
119(Rush et al., 2005), and may even be beneficial for other conditions including tinnitus, chronic
120hiccups and Alzheimer’s disease (see Clancy, Deuchars, & Deuchars, 2013 for review). It is

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121surprising therefore that the implications of vagal involvement in such a wide variety of functions,
122behaviours and conditions are seldom extrapolated beyond the specific field in which the individual
123studies have been conducted. To that end, we bring together the many strands of research conducted
124across a variety of research fields, and provide an interpretative framework through which these
125findings may be understood. This extended neurovisceral integration model (or NIACT),
126emphasises the importance of neurovisceral integration over time, such that the extent to which the
127brain and body are integrated will contribute to eventual mortality.

128

129The overarching aim for this review is to provide a multidisciplinary synthesis and framework
130through which the extensive, yet disparate, body of evidence on the role of HRV in a variety of
131psychological functions, inflammation, illness and disease may be understood. In the sections that
132follow we first describe the theoretical background on which many prior studies have been
133interpreted. Major theoretical models include the neurovisceral integration model (Thayer & Lane,
1342000; 2009) and the polyvagal theory (or PVT) (Porges, 1995; 2011), which characterise the neural
135circuitry underpinning behavioural flexibility to environmental change and social engagement.
136While these models have important implications for mental and physical health, a comprehensive
137model based on the most recently published evidence, linking psychological moments to morbidity
138and mortality remains to be proposed. This is the major rationale for writing the present paper.
139Following this discussion, we provide an interpretative framework that emphasises the link between
140vagal function and HRV, highlighting that all measures of HRV typically index parasympathetic
141nervous system (PNS) function, albeit distinct physiological mechanisms. This section also
142provides an important background for readers who may be unfamiliar with the intricacies of HRV
143research, and the ways in which data has been collected and interpreted (see also Table 1). Our
144model conceptualises HRV as a psychophysiological marker of health and wellbeing, and this
145conceptualisation has wide applicability. We therefore devote the next section of our paper to the
146evidence supporting this claim, highlighting that physical activity, improving diet quality,
147consuming alcohol in moderation and reducing tobacco consumption are all associated with
148increased vagal function. However, health behaviour is not the only factor influencing vagal
149function, leading us to our next section, which focuses on psychological moments including the
150broad constructs of emotion and cognition. We suggest that vagal function may provide the
151physiological foundation on which psychological functioning is supported, while stable changes in
152resting-state vagal function will have direct implications for future health. The following section
153describes some overlapping processes that may link these moment-to-moment (phasic) changes that
154support psychological functioning to stable changes in resting-state vagal function. Several

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155conceptually related processes including self-perpetuating feedback loops and allostatic regulation
156underpinning experience-dependent change are described. A critical regulatory role for the vagus
157nerve over a variety of tightly integrated allostatic systems is described highlighting an important
158role for what has been described as the cholinergic anti-inflammatory reflex. Vagal dysfunction –
159indexed by reduced resting-state HRV – will lead to allostatic load, increasing morbidity and
160mortality, the focus of the following section. The association between vagal function and psychiatric
161disorders and their treatments is described, followed by a discussion on the intimate relationship
162between psychological and physical health and wellbeing, highlighting links between vagal function
163and future health. We then synthesize the body of literature reviewed in preceding sections and
164present our model we label as Neurovisceral Integration Across a Continuum of Time (or NIACT).
165This model emphasizes vagal function as a critical, missing link in prior accounts that have sought
166to link and bridge the gap between psychological functioning and mortality. A variety of theoretical
167conundrums and methodological limitations are then described providing a foundation on which
168future research could be based.

169

170Our paper makes an important contribution to the existing literature on HRV by emphasizing the
171role of a temporal continuum that spans psychological moments through to mortality. Several points
172regarding our review should be noted. First, we describe and discuss studies from diverse fields
173including health psychology, emotion and cognitive science, neuropsychiatry, epidemiology and
174public health. Accordingly, a comprehensive review of the literature in regards to vagal function is
175beyond the capacity of the current paper. Instead, we draw upon recently published reviews within
176each domain and research field, and highlight findings from more recent studies that build upon
177these reviews. Second, we make an important distinction between phasic and tonic HRV,
178emphasizing a principle of demand appropriate responsiveness, in order to better interpret and
179appreciate the significance of increases or decreases in HRV within and between particular groups
180and conditions. Pragmatic and theoretical distinctions are made between HRV collected under
181different recording conditions (i.e. resting state, task and recovery conditions). In this regard we
182propose that resting-state HRV may reflect the combined impact of multiple psychological
183moments, providing the best indication of future health. By contrast, we suggest that task-driven
184activity reflects autonomic responsiveness to that with which the individual is engaged, while
185recovery-related activity may reflect emotional resilience (mental toughness), particularly after a
186stressor. Throughout this paper we emphasize reported effect sizes rather than statistical
187significance where possible, consistent with increasing calls for meta-analytic thinking (Cumming,

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1882014; Lakens, 2013). Effect sizes are interpreted in the context of other similar studies and the way
189in which the authors of specific papers have interpreted their own findings.¹

190

191We now turn our attention to the theoretical background on which our proposal is based, before
192embarking on a targeted review of the literature across several research domains in which vagal
193function has been shown to play an important role.

194

Theoretical Background

195

196Two major theories, the neurovisceral integration model (NIM) (Thayer & Lane, 2000; 2009) and
197PVT (Porges, 1995; 2011), have provided the theoretical framework through which reported
198findings on HRV have been interpreted.

199

200The NIM (Thayer & Lane, 2000; 2009) describes an inhibitory, cortico-subcortical neural circuit
201that integrates brain and body function, and supports a variety of functions including emotion,
202cognition, and social behaviour. Some of the studies supporting links between vagal function and
203these psychological moments are described in following sections. The central autonomic network
204(or CAN) (Thayer & Lane, 2000; 2009) is responsible for the inhibition of medullary
205cardioacceleratory circuits, for controlling psychophysiological resources and appropriate responses
206to environmental change. HRV indexes vagal inhibition of the heart and reflects the primary output
207of the CAN. Neuroimaging studies (B. Allen, Jennings, Gianaros, Thayer, & Manuck, 2014; C.
208Chang et al., 2013a; Thayer, Ahs, Fredrikson, Sollers Iii, & Wager, 2012) have begun to explore the
209association between neural correlates of resting state HRV (B. Allen et al., 2014; C. Chang et al.,
2102013a) as well as HRV reactivity (Thayer et al., 2012) (see also Beissner, Meissner, Bär, &
211Napadow, 2013). These studies have demonstrated that higher resting-state HRV is associated with

231 When necessary, we drew upon the benchmarks provided by Cohen (Cohen, 1988), which can be

24grouped into two families, the *d* family, which relate to standardized mean differences (small, $d = 0.2$;

25medium, $d = 0.5$; large, $d = 0.8$), and the *r* family, which is related to strength of association (small, $r = 0.1$;

26medium, $r = 0.3$; large, $r = 0.5$). When necessary, we drew upon the benchmarks provided by Cohen

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28mean differences (small, $d = 0.2$; medium, $d = 0.5$; large, $d = 0.8$), and the *r* family, which is related to

29strength of association (small, $r = 0.1$; medium, $r = 0.3$; large, $r = 0.5$).

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212 greater resting cerebral blood flow (B. Allen et al., 2014), a finding that may reflect a coordinated
213 physiological substrate for diminishing sympathetic adrenergic inhibition in the nucleus ambiguus
214 and reducing sympathetic vasoconstriction of cerebral arteries during the resting state. By contrast,
215 meta-analysis of HRV reactivity during cognitive, sensory/motor and emotion processing (i.e. task-
216 evoked changes in HRV) reveal a number of regions within the cortical-subcortical pathway
217 including the ventro-medial prefrontal cortex and amygdala (Thayer et al., 2012). According to this
218 model, the CAN shapes brain activity and associated autonomic responses in the body. Therefore,
219 vagal impairment is associated with prefrontal hypoactivity, amygdala hyperactivity and low
220 resting-state HRV contributing to a predisposition to threat perception and inflated negativity biases.
221 By contrast, healthy vagal function will be associated with flexible prefrontal inhibitory control
222 over amygdala function and flexible adaptation to environmental change. Interestingly, resting-state
223 studies (e.g. B. Allen et al., 2014) have also demonstrated that higher resting HRV is associated with
224 lower cerebral blood flow in regions previously implicated in cardiac vagal reactivity (Thayer et al.,
225 2012). More specifically, higher resting HRV is associated with less relative perfusion in left
226 amygdala, left putamen, right hippocampus, left parahippocampal gyrus, left and right insula, and
227 two subregions of the right superior temporal gyrus (B. Allen et al., 2014). Thus, lower resting
228 cerebral blood flow in these areas could be maintaining high levels of resting HRV, while
229 disinhibition of these areas and associated cardioacceleratory circuitry would lead to decreased
230 HRV under challenge. The NIM emphasizes the intimate relationship between brain and body, and
231 suggests that HRV may index ‘top-down’ appraisals, which is mediated by the capacity with which
232 the ventro-medial prefrontal cortex is able to inhibit subcortical pathways.

233

234 The second theory – PVT – is complementary to the NIM, emphasising a phylogenetic shift in the
235 control of the autonomic nervous system (ANS) from the dorsal motor nucleus of the vagus in
236 reptiles to the nucleus ambiguus in mammals (Porges, 1995; 2011). According to the PVT, one
237 consequence of the transition is the emergence of social behaviour including facial expression and
238 vocalisations. The vagus nerve is either myelinated or unmyelinated (i.e. polyvagal), and the model
239 characterises a role for the unmyelinated vagus in phylogenetically older immobilisation behaviours
240 (e.g. extreme terror, neurogenic bradycardia, vasovagal syncope, reproduction, nursing and pair-
241 bonding), while the myelinated vagus is linked to evolutionary younger behaviours (e.g. emotion,
242 social communication and psychophysiological flexibility). It is the myelinated vagus nerve that is
243 linked to HRV and although this aspect of the theory has been challenged (e.g. Berntson, Cacioppo,
244 & Grossman, 2007; Grossman & Taylor, 2007), the psychological and behavioural implications of
245 the theory have been labelled “as something of a sacrament.” (Berntson et al., 2007). The model

339

246describes a trinity of nuclei in the medulla including the dorsal motor nucleus of the vagus
247(DMNX), the nucleus ambiguus (NA) and the nucleus tractus solitarius (NTS). The unmyelinated
248vegetative vagus nerve originates from the DMNX, while the myelinated ‘smart’ vagus originates
249from the NA from which vagal efferent pathways project. The final structure in the trinity is the
250NTS, which is the primary site for termination and integration of many afferent pathways traveling
251from peripheral organs, allowing for subsequent regulation of behaviour.

252

253These theories have helped to contextualise many of the published findings in the literature. Both
254are complementary, and in fact, draw upon Hughlings Jackson’s principle of hierarchical integration
255through inhibition (J. H. Jackson, 1958)

256 in which removal of inhibition ‘permits’ rather than ‘elicits’ increased physiological activity (i.e.
257disinhibition) (Porges, 2011; Thayer et al., 2012). A typical defensive response is associated with a
258reciprocal pattern of vagal inhibition and sympathetic excitation, accompanied by increased heart
259rate and blood flow, and inhibition of the baroreflex, which increases blood pressure (Berntson,
260Cacioppo, & Quigley, 1991). The autonomic nervous system (ANS) may also be co-activated or co-
261deactivated (Berntson et al., 1991; Berntson, Cacioppo, & Quigley, 1993). Co-activation of the
262parasympathetic and sympathetic nervous systems (PNS and SNS) may help mitigate the
263deleterious effects of increased SNS activity (Norman et al., 2011), while sympathetic-
264parasympathetic cardiac deactivation may reflect passive sensory intake (Kreibig, 2010). Recent
265thinking further indicates that vagal activity may actually be withdrawn without activation of the
266SNS (Porges, 2011). This metabolically conservative response to challenge (vagal withdrawal
267without subsequent SNS activation) may also reflect the mood and anxiety disorders during resting
268state (Kemp, Brunoni, et al., 2014a). Both models emphasise different aspects of adaptation and
269engagement. NIM highlights the importance of the prefrontal inhibition over lower subcortical
270pathways in shaping brain activity and subsequent autonomic responses, while PVT emphasises the
271emergent properties of phylogenetically older neural circuits (i.e. “flight”, “fight” or “freeze”) when
272phylogenetically younger circuits critical to social engagement fail to function. According to NIM,
273higher levels of resting-state HRV reflect stronger ‘top-down’ appraisal and prefrontal inhibition of
274cardioacceleratory circuitry. By contrast, the PVT links higher levels of HRV to capacity for social
275engagement and phylogenetically younger behaviours.

276

277**Summary**

278Major characteristics, core components and associated behaviours highlighted in these models are
279summarised in Figure 1. Prosocial behaviour is associated with cortical inhibition of the central

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280nucleus of the amygdala (CeA), activation of the vagus nerve within the nucleus ambiguus—
281increasing vagal tone—facilitate socially engaging facial expressions, leading to positive social
282interactions. The NST receives vagal afferent feedback from the viscera and internal milieu, and this
283information is then directed to cortical structures responsible for the top-down, flexible regulation
284of emotion (Fig 1, black arrows). Increased activation of the vagus nerve therefore facilitates social
285engagement and positive emotion (discussed further below). By contrast, responsiveness to
286environmental challenge (e.g. orienting) and withdrawal from the environment (e.g. fear) will be
287associated with a disinhibition of CeA (the major efferent source for modulation of cardiovascular,
288autonomic and endocrine responses) and vagal withdrawal—decreasing vagal tone—triggering
289fight-flight-or-freeze responses. Again, information relating to the status of the viscera and internal
290milieu are fed back to the nucleus of solitary tract and the cortex, allowing for subsequent
291regulation of the emotion response (Fig 1, grey arrows). Decreased activation of the vagus nerve
292therefore facilitates fight-flight-or-freeze responses and negative emotions. Although both theories
293have important implications for mental and physical health, a comprehensive model linking these
294everyday psychological moments and phasic vagal alterations to morbidity and mortality remains to
295be described; this is the task of the current paper. An interpretative framework for HRV measures
296will now be described after which, relevant studies on HRV from diverse fields of scientific
297endeavour will be discussed.

298

299INSERT FIGURE 1 ABOUT HERE

300

301 **HRV and Vagal Function: An Interpretative Framework**

302

303Vagal modulation of heart rate is fast; it is regulated by acetylcholine, which peaks within 0.5
304seconds and returns to baseline within 1-second (Appelhans & Luecken, 2006; Levy, 1997). By
305contrast, the effects of the SNS are much slower; the SNS is regulated by norepinephrine, which
306peaks only after 4 seconds and then returns to baseline after ~20 seconds (Appelhans & Luecken,
3072006; Levy, 1997). Therefore, measures of HRV that reflect the fast changes provide a surrogate
308measure of vagal function. Although different measures of HRV may reflect distinct physiological
309mechanisms, all typically index SNS function (Reyes Del Paso, Langewitz, Mulder, Roon, &
310Duschek, 2013). A summary and interpretation of common HRV measures across time-, frequency-
311and non-linear domains is provided in Table 1.

312

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313The standard deviation of N-N intervals (SDNN) is a commonly reported, time-domain measure,
314reflecting all cyclic components responsible for variability. SDNN extracted from long-term
315recordings (usually 24-hours) is a robust predictor of adverse cardiovascular events and mortality
316(Hillebrand et al., 2013; Huikuri & Stein, 2013). Commonly reported measures of HRV from short-
317term recordings (2 – 15mins) include the root mean square of successive differences (RMSSD) and
318high frequency HRV (HF-HRV). While RMSSD – a time-domain measure – and HF-HRV are
319highly correlated, the former is less affected by changes in breathing frequency (Penttilä et al.,
3202001; Saboul, Pialoux, & Hautier, 2013), highlighting the utility of this measure during ambulatory
321studies, and in patient populations such as those with an anxiety disorder. Another commonly
322reported measure of vagal function is respiratory sinus arrhythmia (RSA), a measure that combines
323heart rate with respiration data, and like HF-HRV reflects the ebb and flow of heart rate associated
324with respiration. There has also been much research interest in non-linear measures of HRV, which
325assess qualitative properties rather than the magnitude of heart rate dynamics, and may better
326distinguish between groups, however their physiological basis is less clear. For more information on
327collection, extraction and interpretation of these measures, interested readers are referred to past
328reviews on this topic (Appelhans & Luecken, 2006; Berntson et al., 1997; Rajendra Acharya, Paul
329Joseph, Kannathal, Lim, & Suri, 2006; Reyes Del Paso et al., 2013; Shaffer, McCraty, & Zerr, 2014;
330Thayer, Hansen, & Johnsen, 2010a; Thayer, Hansen, Saus-Rose, & Johnsen, 2009).

331

332There is a natural relationship between heart rate and breathing such that heart rate slows on
333expiration and speeds up on expiration. This is a well known phenomenon and has important
334regulatory functions including control of gas exchange at the aveoli (Lehrer & Gevirtz, 2014).
335Arguments over whether or not respiration should be controlled in HRV analyses have tended to
336assume that the direction of causality flows from respiration to cardiac changes. However, the
337causal direction might also flow from cardiac change to respiration (especially under resting state
338conditions), where the heart beat that immediately precedes inspiration triggers inspiratory onset
339(Tzeng, Larsen, & Galletly, 2003); this phenomenon is known as “cardiorespiratory coupling”. In
340this case, controlling for respiration when examining HRV indices will remove variability
341associated with neural control over the heart beat, and therefore some of the variance that
342researchers are interested in studying (Thayer, Hansen, & Johnsen, 2010a). Regardless, RSA is
343considered to accurately reflect vagal modulation of heart rate during resting state recordings and
344most clinical mental stress tasks, when respiration is not expected to vary (J. J. B. Allen, Chambers,
345& Towers, 2007).

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347 While RSA and HF-HRV both index respiratory processes, low frequency HRV (LF-HRV, 0.04-0.15
348 Hz) is thought to reflect blood pressure control mechanisms and vasomotor tone. This component
349 may be associated with baroreflex-mediated blood pressure variations (Moak et al., 2007; Penaz,
350 1978), a reflex by blood pressure sensors in the aorta and carotid artery that modulate blood
351 pressure fluctuations (Eckberg & Sleight, 1992; Lehrer & Gevirtz, 2014). During environmental
352 challenge such as physical activity or stress, LF-HRV may also approximate sympathetic activity,
353 highlighting the importance of recording context when interpreting changes in the LF bandwidth
354 (Shaffer et al., 2014). While researchers have traditionally interpreted the LF/HF ratio as
355 sympathovagal balance, this view is now controversial (see Goldstein, Benth, Park, & Sharabi,
356 2011; Pagani, Lucini, & Porta, 2012; Reyes Del Paso et al., 2013).

357

358 **Summary**

359 In summary, commonly reported measures of HRV include SDNN, an estimate of all cyclic
360 components responsible for variability often reported in studies that have collected data from
361 longer-term recordings (usually 24-hours), and RMSSD and HF-HRV, measures of fast changes
362 associated with vagal modulation, typically reported in studies that have collected data from
363 shorter-term recordings. In the present review, unless stated elsewhere, we focus on these measures
364 and clearly distinguish between different recording contexts, which may impact on conclusions
365 drawn (e.g. heterogeneity of responding during emotion regulation tasks dependent on person-
366 specific characteristics, (e.g. Di Simplicio et al., 2012)). Studies that collect data from short-term
367 recordings often report measures of resting-state HRV. We interpret this psychophysiological
368 marker as a structural bridge between psychological moments and future morbidity (Friedman &
369 Thayer, 1998; Kashdan & Rottenberg, 2010; Kemp, Quintana, Kuhnert, Griffiths, Hickie, &
370 Guastella, 2012b), providing a physiological foundation supporting response to environmental
371 change and challenge, that will both affect and be affected by the cascade of physiological
372 processes subsequently impacting on individual risk for morbidity and mortality. If HRV is a marker
373 of health and wellbeing – as we suggest it is – it should therefore be impacted on by a variety of
374 health behaviours. This is the focus of our next section, after which we begin a review of HRV
375 studies published across a variety research domains, broadly categorised in the fields of psychology
376 and epidemiology.

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Vagal Function and Health Behaviour

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380 Physical health may be improved by increasing physical activity, making changes to dietary habits,
381 consuming alcohol in moderation and reducing tobacco consumption, and all these activities are
382 associated with subsequent improvements in vagal function indexed by increases in HRV, which
383 may subsequently decrease risk for morbidity and mortality (see Thayer, Yamamoto, & Brosschot,
384 2010c for review). Interestingly, a single-item measure of global self-rated health has been
385 associated with HRV measures including SDNN, RMSSD, LF-HRV and HF-HRV (Jarczok et al.,
386 2015), and this association was stronger than any other biomarker including inflammation. Self-
387 rated health is a simple question requiring participants to rate their health in general and has been
388 associated with many health outcomes and shown to predict morbidity and mortality. This study
389 suggests therefore that the extent of central-peripheral feedback is associated with self-rated health,
390 perhaps reflecting the fact that self-rated health may depend on interoceptive ability, supported by
391 afferent vagal projections from peripheral organs to the brain. This bidirectional vagal circuitry –
392 which is indexed by HRV – and the afferent projections, in particular may also provide a theoretical
393 basis through which the effectiveness of other behavioural interventions (e.g. massage, exercise,
394 meditation, yoga and HRV biofeedback) may be understood.

395

396 In a study conducted more than 25 years ago (Hayano et al., 1990), it was concluded that smoking
397 causes an acute and transient decrease in vagal function as measured by RSA, while heavy smoking
398 causes long-term reductions (RSA) as well as blunted postural responses in autonomic cardiac
399 regulation (i.e. postural changes were not observed in heavy smokers as defined by >25 cigarettes
400 per day). Strikingly, more recent research has even reported that non-smokers exposed to
401 environmental tobacco smoke at home or work for more than 2 hours a day (n=80) – relative to the
402 unexposed (n=1034) – display a 2.7% higher heart rate (Felber Dietrich et al., 2007), in addition to
403 a 15% reduction in total power, LF-HRV, low/high frequency ratio and ultralow frequency power of
404 HRV. These findings were not simply acute responses as findings associated with the sleep period
405 were similar to the results from the 24-h measures. Depressed smokers even display decreases in a
406 variety of HRV measures – extracted from recordings during a 5-minute resting period – in
407 depressed patients (N=77) (Harte, Liverant, Sloan, & Kamholz, 2013). These findings are
408 particularly striking considering that depressed patients are already characterised by low HRV
409 (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012a; Kemp et al., 2010; Kemp, Quintana,
410 Quinn, Hopkinson, & Harris, 2014d) (discussed further below). Depressed smokers (n=34) display
411 decreased HF-HRV ($\eta^2_p = 0.11$) and RSA ($\eta^2_p = 0.13$), relative to depressed non-smokers (n=43),
412 even after controlling for demographic and medical characteristics, and medication use (Harte et al.,
413 2013). Another recent study by the same authors (N=62) (Harte & Meston, 2014) demonstrated that

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414successful quitting (n=20) was associated with increases in HRV at follow-up, 4-weeks after patch
415discontinuation. Results from this study were based on RMSSD and HF-HRV extracted from a 3-
416minute baseline period involving presentation of a documentary film (Cohen's *d*'s ranged from 0.50
417to 0.73). By contrast, HRV indices among unsuccessful quitters were generally unchanged across
418time.

419

420Physical activity is associated with a decreased heart rate and increased HRV during the resting
421state, effects that likely contribute to improvements in mental and physical health over the longer
422term (see Carter, Banister, & Blaber, 2003; Thayer, Yamamoto, & Brosschot, 2010c). Thayer and
423colleagues were among the first to report that fit individuals (n=18) – from a group of university
424students aged 17 to 25 years – display greater vagal control of the heart relative to low fit
425individuals (n=16), as determined by time and frequency domain measures of HRV, even after
426controlling for body mass index (BMI) (Rossy & Thayer, 1998). Fitness was determined using a
427questionnaire that estimates VO_{2max} based on subjective report of physical activity, age, body
428composition and sex, while HRV was calculated during a resting baseline period, a face-cooling
429task designed to elicit parasympathetic activity, a reaction time task designed to elicit primarily
430sympathetic activity, a combination task that was designed to elicit a combination of both
431parasympathetic and sympathetic activation, and recovery periods after each task. The key finding –
432increased vagal function in high fit individuals relative to low fit individuals – was observed at
433baseline and across all tasks, demonstrating the robustness of these findings (Cohen's *d* for HF =
4340.61 relating to the main effect of fitness).

435

436A study on the Whitehall II cohort (N=3,328) of older civil servants aged 45-68 years (Rennie et al.,
4372003), showed that moderate and vigorous activity is associated with higher HRV and lower heart
438rate during a 5-minute resting-state, and these findings remained significant after adjustment for
439smoking and alcohol intake. Men whose BMI was greater than 25kg/m^2 and engaged in vigorous
440activity displayed similar HRV levels to normal-weight men who did not engage in vigorous
441activity. Activity levels in this study were determined by a questionnaire that allows for a metabolic
442equivalent (MET) value to be determined, such that 1 MET corresponds to the metabolic energy
443expended lying quietly (equivalent to 1 kcal per kilogram of body weight per hour). Vigorous
444activity was defined as greater than or equal to 5 MET hours per week (Rennie et al., 2003). A
445randomized-controlled study on sedentary young adults (N=149, mean age 30 yrs) reported that 12-
446weeks of aerobic conditioning, but not strength training enhances autonomic control of the heart, as
447determined by decreases in heart rate (3.49 beats per minute or BPM) and increases in HF-HRV

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448(0.25 natural log (ln) msec²) during 10-minutes of quiet rest (R. P. Sloan et al., 2009). These authors
449further reported that 4-weeks of deconditioning following the training period led to these autonomic
450measures returning to pre-training levels.

451

452Research also demonstrates that regular exercisers (n=22) – participants engaging in at least 30
453mins of vigorous activity, three times per week – display a more resilient cardiac stress response
454than irregular exercisers (n=18) ($d = 0.48$) (Hanson, Outhred, Brunoni, Malhi, & Kemp, 2013).
455Participants in this study were required to complete a serial-13's subtraction task, a task adapted
456from the Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993). Regular exercisers
457displayed a resting heart rate of 66 BPM, while irregular exercisers displayed a resting heart rate of
45872 BPM ($d = 0.55$). Interestingly, regular vigorous exercisers also reported feeling less stressed
459during this task. Furthermore, escitalopram, a commonly prescribed selective serotonin reuptake
460inhibitor (SSRI), attenuated the cardiac stress response (heart rate decreased, $d = 0.80$, while HRV
461increased, $d = 0.33$) associated with a mental arithmetic task in irregular exercisers to the same level
462as that displayed by regular exercisers under placebo. These salubrious effects of exercise may even
463extend to the intrauterine environment. A study (N=61) examining the effects of aerobic exercise
464during pregnancy (>30 min of aerobic exercise, 3 X per week) reported beneficial effects on fetal
465cardiac autonomic control of heart rate and its variability (May, Glaros, Yeh, Clapp, & Gustafson,
4662010). This study utilised a dedicated fetal biomagnetometer to record magnetocardiograms to
467detect and separate the fetal cardiac signal from the maternal signal. Fetal heart rate was lower ($d =$
4681.54) and HRV higher (HF-HRV, $d = 0.95$) in the exercise group as compared to foetuses of non-
469exercising women during an active fetal state. In a follow-up study by the same authors, infants
470born to women who exercised during pregnancy display higher RMSSD, LF and HF power (May,
471Scholtz, Suminski, & Gustafson, 2014) indicating that the developing cardiac ANS is sensitive to
472effects of maternal physical activity beyond the womb.

473

474At the other end of the lifespan, greater leisure-time activity, walking distance and walking pace are
475associated with more favourable HRV indices in older adults (N=985) after multivariable
476adjustment (Soares-Miranda et al., 2014). It is worth noting here that this study was conducted in
477adults aged more than 65 years, and caution is advised when interpreting HRV measures collected
478from the elderly as higher levels of HRV may actually reflect abnormal sinus patterns, especially
479when the underlying organisation has not been examined using power spectral methods or other
480graphic methods (Huikuri & Stein, 2013). So in the study with older adults (Soares-Miranda et al.,
4812014), while higher 24-hour SDNN and ultra-low frequency power were prospectively associated

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482with greater total leisure-time, walking distance and walking pace, lower normalized HF-HRV was
483also observed in those that increased walking pace between baseline (1989-1990) and at the follow-
484up period (1992-1993). While this was an unexpected finding, the authors argued that this finding
485might also reflect less erratic HRV in their older cohort. It is noted however, that the authors only
486excluded participants with markedly irregular cardiac rhythms indicated by “extent of irregularity of
487the rhythm or p waves that was [sic] too high for trained personnel to accurately label which beats
488were normal sinus beats.” It is possible that the focus on the elderly in addition to inclusion of those
489individuals with less marked, yet irregular, cardiac rhythms could have contributed to these
490findings. These findings further highlight the utility of short, standardised recordings over 24-hour
491recordings which provide more standardised recordings of resting-state activity.

492

493Vagal function is also improved by dietary changes, including consumption of fruits and vegetables,
494moderate alcohol consumption and intake of omega-3 fatty acids and vitamin D through fish and
495nut consumption (see Thayer, Yamamoto, & Brosschot, 2010c for review). Atlantic salmon served
496three times per week from September to February is associated with significant improvements in
497RMSSD ($d = 0.69$) and heart rate ($d = 0.45$), as well as decreases in state-anxiety ($d = 0.45$) in
498forensic inpatients ($N=95$) (Hansen et al., 2014). This study also reported a positive relationship
499between RMSSD and vitamin D status ($r = 0.27$). A recent meta-analysis (Xin, Wei, & Li, 2013) on
50015 randomised controlled trials ($N=692$) reported that short-term term effects of fish-oil
501supplementation (6-24 weeks) increased HF-HRV ($d=0.30$), while effects on other measures
502including SDNN and RMSSD were not significant. The authors suggested that this observed
503increase in HRV may underpin the antiarrhythmic and other clinical effects of fish oil. Other
504research (Soares-Miranda et al., 2012) has demonstrated that trans-fatty acid consumption – and
505higher plasma phospholipid and erythrocyte membrane 18:2 TFA (*trans*-18:2) consumption in
506particular – is associated with specific, less favourable indices of HRV in young ($N=160$) and older
507($N=461$) adults. It is relevant to note here that *trans*-18:2 is also associated with increased risk of
508coronary heart disease and sudden cardiac arrest (e.g. Lemaitre et al., 2006).

509

510Finally, there is increasing evidence for the beneficial effects of a variety of complementary and
511alternative medical therapies (e.g. meditation, acupuncture) on vagal function (see Oke & Tracey,
5122009 for review). A course of integrative mind-body training (IBMT), a technique adapted from
513traditional Chinese medicine that incorporates meditation and mindfulness practices, leads to a host
514of physiological changes ($N=43$; $n=20$ in the IBMT group) including improved vagal function
515during and after 5-days of training in this technique. As little as 20 minutes of practice per day

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516lowered heart rate ($d = 1.65$) and sweat response, increases HRV ($d = 1.44$), and results in deeper
517and calmer breathing relative to a relaxation control group (Tang et al., 2009). Another study on the
518impact of intensive 10-day Vipassana meditation (N=36) reported similar increases in the
519normalised, HF-HRV ($d = 0.57$) during meditation following the retreat, consistent with prior
520studies including that of Tang and colleagues (Tang et al., 2009; Wu & Lo, 2008). Decreases in the
521LF-HRV were also observed ($d = 0.73$), a finding that has been linked to vagally-mediated,
522baroreflex outflow (Reyes Del Paso et al., 2013). These findings were interpreted in the context of
523positive and full immersion in an activity, a psychological phenomenon labelled as ‘flow’
524(Csikszentmihalyi, 2002).

525

526**Summary**

527These studies highlight the beneficial effects of a variety of health behaviours on vagal function,
528reinforcing the conceptualisation of HRV as a psychophysiological marker of health and wellbeing.
529This is an important facet of our model (described below), which links activities and behaviours that
530may increase or decrease risk for future morbidity and mortality. We note however, as in most
531scientific endeavours, that contradictory evidence has also been reported. For example, weak and
532inconsistent associations have been reported for HRV and physical activity, alcohol and smoking in
533a large cross-sectional study based on 1671 participants (aged 45 – 83 years), recruited as part of the
534prospective, population-based Cardiovascular Disease, Living and Ageing in Halle (CARLA) study
535(Kluttig et al., 2010). This study actually concluded that there may be no, true causal association of
536behavioural factors with HRV, however, this study was associated with a variety of limitations
537including a questionnaire-based measure to assess physical activity levels, which may be less
538sensitive than more objective measures of regular exercise, restriction of analysis on physical
539activity to a subgroup of participants who were physically active thereby minimising sample
540variability, and focusing on an older sample aged between 45 and 83 years, which may be
541confounded by age-related decreases in HRV (Agelink et al., 2001; Jennings & Mack, 1984;
542Yeragani, Sobolewski, Kay, Jampala, & Igel, 1997) (see also Thayer, Yamamoto, & Brosschot,
5432010b). It is also possible that experimental control over respiratory parameters may confound the
544visceral-medullary feedback system and shift respiratory parameters (Porges, 2011). Despite these
545limitations, this study (Kluttig et al., 2010) indicates that behavioural factors are not the only factors
546influencing vagal function. In this regard, we now turn our attention to the relationship between
547vagal function, emotion and its regulation.

548

549

Vagal Function and Psychological Moments

550

551 Vagal Function, Emotion and its Regulation

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553 Although research on emotion has increased exponentially over the last decade, the term ‘emotion’
554 remains ill-defined, and this situation has led to an “intellectual stalemate” (LeDoux, 2012) leading
555 some to liken the situation to the Hundred Years’ War between England and France (Lindquist,
556 Siegel, Quigley, & Barrett, 2013). We suggest here that this stalemate may, in part, relate to modern
557 neuroscientific research focusing on the brain, while the contributions from the body have been
558 largely sidelined. Bidirectional communication between the brain and body play an important role
559 in emotion and its regulation, such that the brain impacts on the body via visceral efferent pathways,
560 and the body impacts on the brain through afferent feedback (Kemp, Krygier, & Harmon-Jones,
561 2014b). It is possible therefore that the extent to which emotion is able to be effectively regulated
562 will depend on the extent of central-peripheral neural feedback and CAN-ANS integration, as
563 indexed by HRV (Thayer & Friedman, 2002; Thayer & Lane, 2009). However, emotion is typically
564 interpreted through the lens of the SNS (Porges, 2011), as first described by Cannon (Cannon, 1927)
565 and subsequently by Selye (Selye, 1936; 1956). Consistent with this approach, modern research has
566 generally focused on cortical arousal using a variety of neuroimaging techniques to assess brain
567 function, with little attention to the distinction between excitation and inhibition (Porges, 2011).
568 However, the theoretical frameworks – NIM and PVT – described above, emphasise an important
569 inhibitory role over cardioacceleratory structures allowing for the regulation of subsequent
570 behaviour.

571

572 An important component of emotion and social cognition is the capacity to determine what the
573 other is thinking by recognizing and interpreting subtle facial cues, which subsequently guide
574 emotional and behavioural responses to others in the environment. An association between HF-HRV
575 extracted from 5-minute resting-state recordings and performance on a subsequent emotion
576 recognition task ($r = 0.26$) has been reported ($N=65$) (Quintana, Guastella, Outhred, Hickie, &
577 Kemp, 2012). This study highlighted for the first time, a role for vagal function in the ability to
578 recognise emotion expressions from the eye region. Consistent with PVT (Porges, 2011), these
579 findings indicate that emotion perception is facilitated by a calm physiological state and effective
580 inhibition of the SNS. This possibility is supported by an earlier study (Bal et al., 2009) on children
581 with autism spectrum disorders (ASD) ($n=33$), a condition characterised by impairments in social
582 functioning. This earlier study reported that children with ASD display decreased resting HRV (as

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583measured by RSA during the resting state) ($d=0.48$) and increased heart rate ($d=0.55$), relative to a
584control group of typically developing children ($n=45$), reflecting a generalised, psychophysiological
585state that may inhibit capacity for social interaction. HRV in this study (Bal et al., 2009) was
586extracted from a 2-minute baseline period in which participants were in a generally stable and calm
587state. Consistent with our later study in undergraduate students (Quintana et al., 2012), the authors
588also observed that higher RSA was associated with faster emotion recognition.

589

590An increasing body of research has highlighted a relationship between resting-state HRV and
591measures of positive mood (Geisler et al., 2010; Geisler, Kubiak, Siewert, & Weber, 2013; Oveis et
592al., 2009; Z. Wang, Lü, & Qin, 2013) (but see Silvia, Jackson, & Sopko, 2014). A study on 80
593young adults (Oveis et al., 2009) reported that RSA – measured during a 90-sec resting state
594(RSA_{REST}) – is related to self-reported extraversion ($r = 0.37$), agreeableness ($r = 0.22$), optimism (r
595= 0.27), state positive affect ($r = 0.36$) and lower neuroticism ($r = -0.21$). Importantly, RSA_{REST} was
596not associated with increased positive emotion, or stimulus-specific emotion, in response to
597compassion-, awe-, or pride-inducing stimuli. Nor was RSA_{REST} associated with negative mood. A
598study on 172 university student participants demonstrated that HF-HRV – measured during a 7-min
599resting state – was associated with subjective wellbeing ($r = 0.16, 0.17$) (Geisler et al., 2010). This
600study further reported that the relationship between HRV and wellbeing was mediated by emotion
601regulation strategies, an observation we discuss further below. A more recent study by the same
602authors (Geisler et al., 2013) on 125 undergraduate students reported that HF-HRV – again,
603measured during a 7-min resting state – is correlated with self-reported social behaviours including
604engagement ($r = 0.33$), social-support seeking ($r = 0.23$), social integration ($r = 0.29$) and social
605acceptance ($r = 0.25$). Another study (Z. Wang et al., 2013) on 98 young adults reported that HF-
606HRV – measured during a 5-min baseline period – was correlated with positive ($r = 0.31$), but not
607negative ($r = -0.03$) affectivity. A recent study (Silvia et al., 2014) however, reported that HF-HRV,
608RMSSD and other time-domain measures of HRV measured during a 6-minute ‘vanilla’ baseline do
609not predict any measures of positive mood states including personality traits and a variety of self-
610reported, positive emotions ($N=239$). (Effect sizes of observed correlations ranged from zero to
611small.) These null findings highlight the limitations of between-subject designs, which are
612characterised by less optimal experimental control.

613

614Several published studies benefiting from repeated assessment of the same individuals are worth
615noting here. The first study ($N=65$) (Kok et al., 2013) involving random allocation of participants to
616a course in loving-kindness meditation (LVK) or control reported an increase in positive emotions

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617in those allocated to LVK, an effect that was moderated by baseline vagal activity. Two-minute
618recordings were collected during the resting state to extract HF-HRV and RSA before the LVK
619workshop. This study further observed that increased positive emotions led to additional increases
620in vagal activity (resting-state HRV was collected a second time following the LVK intervention), a
621finding mediated by increased perceptions of social connections. Extending on findings reported in
622their earlier study (Kok & Fredrickson, 2010), these authors built a parallel-process mediation
623model to test the hypothesised bidirectional causal chain between emotion and vagal function.
624Importantly they ruled out five additional alternative models that could have potentially explained
625their findings. The authors conclude that positive emotions build physical health, and that the
626bidirectional relationship between emotion and vagal function supports a conceptual model
627involving a self-sustaining, upward-spiral dynamic. It is possible that this bidirectional relationship
628also applies to negative emotions in which negative emotion and vagal function may lead to a self-
629sustaining, downward-spiral dynamic perhaps contributing to impaired emotional regulation
630capacities characteristic of many psychiatric disorders. Another study on 60 healthy adults
631demonstrated that deactivated positive affect (i.e. relaxed, content, even-tempered, calm), but not
632activated positive affect (i.e. dynamic, active, awake, brisk, delighted) is associated with higher
633nocturnal vagal tone (HRV: $r = 0.28$; heart rate: $r = -0.36$) (Schwerdtfeger, Friedrich-Mai, &
634Gerteis, 2014). In this study, measures were extracted from ECG data collected between 1 to 5am.
635Surprisingly, no association between negative affect and cardiac variables were obtained in that
636study (Schwerdtfeger et al., 2014). The authors interpreted their findings along a causal pathway
637from positive emotion to health, in the context of other evidence (Ben-Dov et al., 2007) that
638reported elevations in nocturnal heart rate and attenuation in its variability increase risk for all-cause
639mortality.

640

641Interestingly, while *positive mood* appears to be associated with increased vagal function, *positive*
642*emotions* are associated with vagal withdrawal, highlighting the principle of context appropriate
643responsiveness. Research has demonstrated that recall and experiential reliving of happiness is
644associated with an increase in heart rate and decrease in its variability (Rainville, Bechara, Naqvi, &
645Damasio, 2006). This study (N=43) also reported an increase in heart rate for all emotions (anger,
646fear, happiness and sadness); only fear and happiness displayed decreases in HF-HRV. In another
647study, the cardiorespiratory effects of musically induced emotions were related to the “arousal”
648dimension, rather than the “valence” dimension of emotion (Nyklíček, Thayer, & Van Doornen,
6491997), providing one explanation in which to understand the effects of positive emotions – rather
650than mood – on vagal function. A more recent study on 83 healthy, young-to-middle aged

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651participants (Overbeek, van Boxtel, & Westerink, 2012) reported strong overall heart rate
652deceleration from baseline level to presentation of pictures as well as film fragments ($\eta^2_p = 0.626$),
653while HRV measures (and frequency domain measures in particular) displayed a decrease (η^2_p
654ranged from 0.077 to 0.229) during exposure to film fragments – but not to pictures – regardless of
655the specific emotion. These heart rate decelerations reflect an ‘orienting’ response that facilitates
656information processing of external stimuli (note that heart rate was increased during recall and
657experiential reliving of emotion, (Rainville et al., 2006)), while changes in HRV measures were
658observed to relate to increased respiration rate during presentation of films ($\eta^2_p = 0.457$). Heart rate
659and HRV are also particularly sensitive to anxiety and stress (see Fig 2); for example, strong
660increases in heart rate ($d = 4.476$) and decreases in HRV ($d = 2.895$) are observed during completion
661of a serial-thirteens subtraction task (Hanson et al., 2013; Kemp, Outhred, et al., 2014c), a
662commonly used stressor (Kirschbaum et al., 1993). These findings highlight the importance of
663distinguishing between an emotion, especially positive emotions, and mood, a relatively longer-
664lasting and more diffuse emotional state.

665

666INSERT FIGURE 2 ABOUT HERE

667

668It is also important to note here that cardiovascular activation to negative emotions lasts longer than
669positive emotions (Brosschot & Thayer, 2003). This delayed recovery following the experience of
670chronic negative emotions may be a critical factor linking negative emotions (‘stress’) to physical
671disease. Interestingly, individuals with high implicit anxiety following a stressor display increased
672heart rate and greater stressor-induced decreases in HRV (Verkuil, Brosschot, & Thayer, 2014), and
673these findings were independent of conscious anxiety. Chronic worry, anxiety and hypervigilance –
674core characteristics of the anxiety disorders, and generalized anxiety disorder in particular – may
675contribute to prolonged cardiovascular activation leading to observed chronic alterations in heart
676rate and HRV (e.g. Kemp, Brunoni, et al., 2014a), which may trigger a host of adverse downstream
677processes (as reviewed in following sections).

678

679Resting heart rate and HRV however, do not simply reflect emotional state per se. In fact, a body of
680research indicates that resting-state measures contribute to an individuals capacity for executive
681control in the face of emotional stimuli (Geisler et al., 2010; Kryptos, Jahfari, van Ast, Kindt, &
682Forstmann, 2011) (see also Geisler et al., 2013; Meule et al., 2013). A study on 172 university
683student participants demonstrated that HF-HRV – measured during a 7-min resting state – was not
684only associated with subjective wellbeing ($r = 0.16, 0.17$), but that these effects were completely

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685mediated by executive emotion regulation strategies such as inhibition, planning and mental shifting
686(Geisler et al., 2010). This study concluded that their findings provide support for the proposal that
687resting HRV indexes self-regulatory strength, involving the ability to exert self-control and override
688one's dominant response tendencies. Another study on 54 young adult participants reported that
689response inhibition during an emotional stop-signal task was slower in individuals low on HRV
690(baseline RMSSD from a 10-min ECG recording) ($n=27$), relative to those high on HRV ($n=27$) (d
691= 0.91), in the presence of negative emotion, but not neutral stimuli (Kryptos et al., 2011).
692Response inhibition is a core feature of executive control and the capacity for flexible behaviour in
693response to a changing environment. This study suggests therefore, that individual differences in
694HRV may underpin differential cognitive control processes, including the inhibition of motor
695responses, in the presence of emotional stimuli.

696

697Studies have also demonstrated that HRV is modulated during tasks requiring emotion regulation,
698such that HRV increases reflect successful engagement of cognitive inhibitory processes, while
699decreases may reflect impairment in these processes. When women engage in an initial negative
700task, HF-HRV increases during discussion of an ongoing marital disagreement (Smith et al., 2011),
701compared to that collected during a baseline condition, a finding that may reflect greater self-
702regulatory effort associated with maintaining marital quality. By contrast, women who engage in an
703initial neutral or positive task displayed a decrease in parasympathetic activity during the
704disagreement, a response that is a characteristic cardiac response to stress. Baseline HF-HRV also
705positively correlates with wives' self-reports of relationship depth and positivity. Similarly, baseline
706HF-HRV is associated with husbands' self-reports of positivity, and is also, inversely associated
707with self-reports of negativity. Intriguingly, a positive correlation between husbands' and wives'
708resting HF-HRV is also observed suggesting synchronisation between individual physiological
709states, an intriguing possibility that deserves further study. In another study on 33 individuals from
710the general population (Di Simplicio et al., 2012), individuals scoring low on the personality trait of
711neuroticism displayed increases in HF-HRV when down-regulating negative affect during viewing
712of negative pictures, relative to passive image viewing. By contrast, individuals scoring high on
713neuroticism displayed an opposite tendency. The authors concluded that reductions in HF-HRV
714during cognitive regulation of negative emotional stimuli may reflect a distinct impairment in
715cognitive inhibitory responses over negative affect, consistent with reduced flexibility in vagal
716function. Another study (Berna, Ott, & Nandrino, 2014) on 63 undergraduate students demonstrated
717that while HF-HRV decreases from baseline to film-elicited negative emotion (anger), it increases
718during recovery, but these increases were only observed in individuals categorised as having low

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719 levels of emotion regulation difficulties (ERDs). Those with high levels of ERDs displayed a
720 persistent low HF-HRV during recovery, which may again relate to impairment in regulatory
721 processes and low-levels of resilience to fleeting emotion. Finally, individuals with higher tonic
722 HRV display phasic HRV enhancement during selective attention (when task-related stimuli are
723 superimposed on fearful distractor stimuli), however, those with lower tonic HRV display phasic
724 HRV suppression (N=77) (G. Park, Vasey, Van Bavel, & Thayer, 2014b). These findings provide
725 direct support for a relationship between tonic and phasic HRV, such that higher tonic HRV supports
726 greater self-regulatory effort indicated by phasic HRV enhancement, while lower tonic HRV may
727 contribute to autonomic stress responses indicated by phasic HRV suppression.

728

729 **Summary**

730 In summary, research demonstrates that higher resting HRV is associated with more positive mood
731 states, and capacity for more flexible cognitive processing that facilitates emotion regulation. By
732 contrast, lower resting HRV is associated with hypervigilant and impaired cognitive processing that
733 is detrimental to subsequent emotion regulation. However, phasic decreases in HRV are also a
734 characteristic feature of psychological stress, highlighting an important distinction between phasic
735 and tonic (resting-state) HRV recordings. Phasic HRV increases or decreases may also be displayed
736 under the same condition (e.g. acute stress) reflecting either regulation strategies or an autonomic
737 stress response, respectively, highlighting person-specific responsiveness. Research into
738 understanding individual variability in phasic HRV alterations and associated recovery periods has
739 only begun recently, and provides a fertile area for future research activities. In this section we
740 highlighted a role for HRV in emotion regulation, and this discussion provides a perfect segue to the
741 association between HRV and cognition, a topic we turn our attention to next.

742

743 **Vagal Function and Cognition**

744 Recent epidemiological research has demonstrated that low levels of cardiovascular health are
745 associated with future cognitive impairment (Reis et al., 2013; Thacker et al., 2014). The American
746 Heart Association has defined the concept of ideal 'cardiovascular health' (Lloyd-Jones et al., 2010)
747 by the presence of ideal health behaviours, which for adults includes not smoking, a body mass
748 index <25 kg/m², moderate physical activity for more than 150 min/wk (or vigorous activity for
749 more than 75 min/wk), pursuit of a diet consistent with current guideline recommendations, and
750 ideal health factors (untreated total cholesterol <200 mg/dL, untreated blood pressure <120/<80 mm
751 Hg, and fasting blood glucose <100 mg/dL). Epidemiological studies on large samples of young
752 (Reis et al., 2013) and older (Thacker et al., 2014) participants now suggest that efforts to improve

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753cardiovascular health consistent with the American Heart Association strategic goals for 2020 and
754beyond (Lloyd-Jones et al., 2010) may have important implications for cognitive outcomes later in
755life, including delaying onset of dementia.

756

757The NIM (Thayer et al., 2009) provides a neuropsychophysiological framework in which these
758epidemiological findings may be understood. This model describes the CAN, which highlights a
759tight linkage between cardiovascular and cognitive function. The functional integrity of the CAN is
760indexed by HRV, which reflects the inhibitory capacity of the prefrontal cortex. A study on 311
761physically disabled, community-dwelling women aged 65 and older (Dae Hyun Kim et al., 2006),
762reported that reduced RMSSD, NN50, and HF power – extracted from 2-hours of ECG recordings
763during resting state – was associated with prevalent cognitive impairment according to the Mini-
764Mental State Examination. These findings were reported after adjusting for relevant demographic
765and clinical characteristics including subclinical inflammation (serum IL-6). Strikingly, this study
766reported that reduced high-frequency power was associated with a 6.7-fold increase in odds for
767cognitive impairment. RMSSD and NN50 were associated with 3.37- and 3.29-fold increase in
768odds, respectively. A major limitation of this study however, was its cross-sectional design, which
769did not allow the authors to determine whether reduced HRV preceded the development of
770cognitive impairment or how HRV changes over time and subsequently affects cognitive function.

771

772Other research however, has shown that experimental modulation of HRV impacts on prefrontal
773cognitive function (e.g. Albinet, Boucard, Bouquet, & Audiffren, 2010; Hansen et al., 2004),
774resonating with Aristotelian thinking on the functional role of the heart (C. G. Gross, 1995). In an
775early study (Hansen et al., 2004) on 37 males from the Royal Norwegian Navy, physical training
776involving 3 hours per week of aerobic exercise was associated with increased HF-HRV ($d = 0.65$) –
777measured during a 5-min resting state – faster reaction times and more true positive responses on
778tests of executive function as determined through a continuous performance task and working
779memory test. This study involved within- (i.e. repeated assessment, before and after 4-weeks of de-
780training or continued training) and between-subjects factors (i.e. participants were allocated into
781either a trained- or a detrained group based on application for further duty). This study was the first
782to suggest that HRV modulates prefrontal cognitive function. More recently, a randomised-
783controlled study on 24 elderly participants reported that a 12-week aerobic training program
784increased measures of time and frequency domain HRV (d 's ranged from 0.27 – 0.53) – measured
785during a 5-min resting state – and executive function, relative to a 12-week stretching program
786(Albinet et al., 2010). Aerobic training involved activities such as walking, circuit-training, step and

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787 gradual running, while stretching involved enhancing flexibility, balance and body consciousness.
788 While HRV increased from pre-training to post-training in the aerobic group, it decreased for the
789 stretching group ($d = -0.42$); findings associated with a small (for time-domain measures) to
790 moderate (for HF-HRV) effect sizes. Strikingly, executive function – measured by the Wisconsin
791 Card Sorting Test – improved in the aerobic group, a finding associated with a moderate effect size
792 ($d = 0.47$), while performance was actually worse for those in the stretching group ($d = 0.27$, small
793 effect). Together these studies (Albinet et al., 2010; Hansen et al., 2004) provide important evidence
794 for the impact of exercise on cognitive ability.

795

796 Individuals with higher resting state HRV have been shown to display greater capacity for memory
797 suppression, when required to do so (Gillie, Vasey, & Thayer, 2014), reinforcing a role for HRV in
798 executive function and individual differences in inhibitory control. This study demonstrated that
799 higher HF-HRV – measured during a 5-min resting state – is associated with greater control over
800 memory (η^2_p ranged from 0.05 to 0.14), based on a think/no-think (TNT) paradigm (Anderson &
801 Green, 2001). This task involves learning a list of cue-response word pairs (e.g. “Tape-Radio”) and
802 then, participants are presented with cues studied earlier (e.g. “Tape”) and either remembering the
803 response word (“Radio) in the think trials, or preventing the recall of the response word in the non-
804 think trials. This no-think trial requires successful memory suppression supported by executive
805 control regions of the brain including the prefrontal cortex, which down-regulate activity in the
806 hippocampus to stop memory retrieval. This capacity for memory suppression has important
807 clinical implications. For example, post-traumatic stress disorder is characterised by intrusive
808 memories, which play a role in the severity and course of the disorder. The ability to exert control
809 over unwanted memories is therefore an important factor maintaining psychological health (Gillie et
810 al., 2014) (see also: G. Park, Thayer, Vasey, & Van Bavel, 2014a).

811

812 So what might be the mechanism underlying these surprising associations between vagal function
813 and cognition? Research has demonstrated a suite of molecular and neurochemical alterations to be
814 triggered by vagal nerve stimulation (VNS) including release of norepinephrine within the LC,
815 subsequently stimulating α_1 -adrenergic receptors in the dorsal raphe nucleus leading to serotonin
816 release (Cheyuo et al., 2011; Manta, Dong, Debonnel, & Blier, 2009). Norepinephrine and serotonin
817 – both of which stimulate neurogenesis – are projected extensively to many parts of the brain
818 (Cheyuo et al., 2011; Follesa et al., 2007). Neurogenesis involves increased expression of brain-
819 derived neurotrophic factor (BDNF) (Biggio et al., 2009; Follesa et al., 2007), a key molecule
820 involved in the regulation of metabolic efficiency, eating behavior, synaptic plasticity, and learning

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821and memory (Gomez-Pinilla, 2008). The vagus nerve also makes extensive polysynaptic projections
822to the thalamus, hypothalamus, the limbic system, and the cerebral cortex (Cheyuo et al., 2011;
823Henry, 2002) via the NTS in the brainstem. These alterations may underpin the improvements in
824cognitive function (and mood) that have been associated with vagal nerve stimulation (Groves &
825Brown, 2005; Vonck et al., 2014).

826

827**Summary**

828In summary, these studies have highlighted a key role for vagal function in cognitive capacity,
829particularly inhibitory control and executive functions including attention and working memory. In
830fact, this role may underpin recent findings linking HRV to time perception (Celleni et al., 2015), an
831ability crucial to adaptive behaviour and social functioning. The link between vagal function and
832cognition also has important implications for more effective treatments of psychiatric disorders,
833conditions that are characterised by cognitive impairment (e.g. Quinn, Harris, & Kemp, 2012). The
834role of vagal function in psychiatric illness is the issue we turn to next.

835

836 **Vagal Function: A Critical Link between Psychological Moments and** 837 **Mortality**

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839Our model – outlined below – highlights an important role for vagal function across a continuum of
840time, linking psychological moments to increases or decreases in risk for morbidity and mortality.
841Vagal function provides the physiological foundation on which psychological functioning is
842supported, while stable changes in resting-state vagal function will have direct implications for
843future health. Our framework distinguishes between phasic and tonic vagal function, such that
844phasic increases and decreases both reflect demand appropriate responsiveness to change in the
845environment, while chronic increases and decreases typically reflect healthy and unhealthy vagal
846function, respectively. It must be noted however, that context is critical to understanding potentially
847contradictory findings. For instance, phasic responding under acute stress may be either increased
848or decreased depending on whether the individual engages in self-regulation or experiences an
849autonomic stress response, while caution is advised over interpreting high resting-state HRV in the
850elderly, which may reflect abnormal chaotic cardiac activity, especially if the data are not inspected
851carefully. In summary, phasic HRV changes will reflect ongoing vagal changes associated with
852psychological moments, while chronic vagal function – indexed by standardised, resting-state

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853 recordings – will index longer-term adaptations that will be dependent on person-specific
854 vulnerabilities, accumulative life events – especially chronic stress – and age (over which vagal
855 function decreases markedly). So what might be the processes linking short-term phasic changes to
856 longer-term individual differences in resting state vagal function? Several conceptually related
857 processes including self-perpetuating feedback loops and allostatic regulation will now be briefly
858 described below.

859

860 The experience of contextually appropriate emotions – rather than, for example, maximising the
861 experience of positive emotions over negative ones – is considered to reflect healthy psychological
862 functioning (see Kashdan & Biswas-Diener, 2015 for discussion). In fact, negative affective states
863 typical of those experienced in everyday life have been shown to have a variety of cognitive (e.g.
864 improved memory performance), motivational (e.g. increased perseverance) and interpersonal
865 benefits (e.g. increased concern for others) (Forgas, 2013). However, experience-dependent change
866 in the neural circuitry of emotions may also lead to lasting affective dispositions (affective
867 plasticity) through upward or downward spirals of positivity or negativity, respectively (Garland et
868 al., 2010). Negative emotions may become a source of dysfunction in combination with primitive
869 thought – action tendencies (flight-fight-freeze responses) may serve to self-perpetuate
870 physiological reactivity and trigger destructive behaviours toward self and others (Garland et al.,
871 2010). By contrast, positive emotions may serve to counter downward spirals of negativity,
872 providing a ‘bulwark against the stress of life’ and reducing the impact of distress (Garland et al.,
873 2010). It is important to highlight here that this approach does not ignore the benefits of mild and
874 temporary negative emotions; rather it highlights the self-perpetuating nature of negative emotions
875 if not situated in a broader context in which the impact of negative emotions are balanced by
876 positive features of the situation (Eric Garland, March 2016, personal communication). Parallel
877 lines of evidence in physiology have described a related concept in physiology, allostasis, which
878 refers to the multisystemic adaptations required to maintain homeostasis allowing the body to cope
879 with environmental challenge (McEwen, 1998).

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881 The concept of allostasis describes the process of achieving stability through change, involving
882 physiological adaptation to changing environmental conditions underpinned by coordinated
883 responses within a tightly integrated network of neural, endocrine and immune systems (Danese &
884 McEwen, 2012; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; McEwen, 1998). Psychological
885 stress will elicit activation in the amygdala, triggering the locus coeruleus to induce a state of
886 alertness and focused attention, and the paraventricular nucleus of the hypothalamus, which then

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887coordinates a neuroendocrine response to stress sustaining increased metabolic demand. Activation
888of the SNS will trigger bodily responses characterized as the “fight or flight response”, and an
889immune response (inflammation) to protect the body against tissue damage should it occur. While
890adaptations to environmental challenge over the short-term provide an organized and coordinated
891response that facilitates survival over the longer-term, chronic or repeated exposure to stressors will
892have detrimental physiological consequences. Enduring activation of allostatic systems will lead to
893structural and functional abnormalities in the nervous system, elevations in inflammatory levels and
894chronic activation of the HPA axis that may lead to downregulation of anti-inflammatory pathways.

895

896We highlight here the critical regulatory role that the vagus nerve has over a variety of allostatic
897systems including sympathetic nervous system (Porges, 2011), inflammatory processes (Huston &
898Tracey, 2010), the HPA axis (Porges, 2011), and glucose metabolism (Pocai, Obici, Schwartz, &
899Rossetti, 2005) (P. Wang et al., 2008) (see also: Thayer & Sternberg, 2006). While emotional
900influences over allostatic systems have been emphasized in the links between emotion, morbidity
901and mortality (Kiecolt-Glaser et al., 2002), the regulatory role of the vagus in metabolic
902homeostasis and control of innate immune responses has generally been ignored when allostatic
903processes are described. One mechanism through which the vagus regulates downstream allostatic
904systems is the “cholinergic anti-inflammatory reflex” (Huston & Tracey, 2010; Tracey, 2002; 2007;
905Tracey & Pavlov, 2012). This neural mechanism involves the inhibition by acetylcholine – the
906principle parasympathetic (vagal) neurotransmitter – of macrophage activation and synthesis of
907tumor-necrosis factor (TNF) at the alpha-7 nicotinic acetylcholine receptor sub-unit that is
908expressed on monocytes, macrophages and other cytokine producing cells (Huston & Tracey, 2010;
909H. Wang et al., 2003). It plays a key role in detecting cytokines and pathogen-derived products by
910the afferent (sensory) vagus nerve, and the regulation and control of cytokine release by the efferent
911(motor) vagus nerve. Vagal impairment – indexed by tonic, resting-state HRV reductions – will
912therefore lead to overstimulation of these allostatic systems, a condition known as ‘allostatic load’
913(McEwen, 1998), characterized by excessive proinflammatory cytokine activity, subsequently
914contributing to prolonged infections, delayed wound healing, and ill-health from a host of
915conditions and diseases including obesity, diabetes, atherosclerosis, osteoporosis, arthritis,
916Alzheimer's disease, periodontal disease, cancer, frailty and disability (Kemp & Quintana, 2013;
917Thayer & Lane, 2007; Thayer, Loerbroks, & Sternberg, 2011; Thayer, Yamamoto, & Brosschot,
9182010c).

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920A study by Thayer and Fischer (Thayer & Fischer, 2009) reported the first evidence for this
921cholinergic anti-inflammatory pathway in healthy humans while controlling for SNS activity. Vagal
922function (indexed by 24h HRV as measured by RMSSD) was inversely related to inflammation,
923indexed by plasma levels of C-reactive protein (CRP) ($r = -0.19$; $r = -0.12$, partial correlation) and
924white blood cell counts (WBC) ($r = -0.16$; $r = -0.13$, partial correlation). Importantly, vagal function
925remained inversely associated with markers of inflammation (CRP, WBC) after controlling for SNS
926activity, which could involve either pro- or anti-inflammatory responses. Strikingly, the difference
927in CRP between the lowest quartile of RMSSD and the highest quartile of RMSSD was larger than
928previously reported differences between current smokers and non-smokers. A more recent study by
929Thayer and colleagues demonstrates that HRV actually predicts CRP levels four years into the
930future ($r = -0.34$; $r = -0.20$, partial correlation), thus providing the first prospective data showing
931that low HRV predicts increased chronic inflammation over a period of years in healthy working
932individuals (Jarczok, Koenig, Mauss, Fischer, & Thayer, 2014).

933

934**Summary**

935Vagal function may reflect the critical missing link between psychological moments and mortality,
936because of its dual role in supporting psychological functions and in regulating downstream
937changes in allostatic systems that may subsequently increase or decrease risk for morbidity and
938mortality. As described earlier, resting state HRV is correlated with emotional traits such that higher
939HRV is associated with positive mood states (Kok et al., 2013; Kok & Fredrickson, 2010; Oveis et
940al., 2009). Studies investigating the impact of meditation practice on HRV, for example (Kok et al.,
9412013; Kok & Fredrickson, 2010), have already provided evidence that HRV may provide a
942psychophysiological foundation for self-sustaining, upward-spirals of positivity. We suggest here
943that vagal function may also support self-sustaining, downward spirals leading to persistent
944negative mood, and increases in allostatic load, morbidity and mortality.

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Vagal Function, Morbidity & Mortality

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948**Vagal Function, Psychiatric Disorders & their Treatments**

949

950The association between psychiatric disorders and HRV has attracted much research attention over
951several decades. PVT (Porges, 2011) has linked vagal nerve outflow to social engagement,
952impairment in which is a major characteristic of psychiatric disorders. Related features including

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953 flattened affect, poor eye gaze, attenuated facial expressions, lack of prosody, and hyperacusis may
954 also be underpinned by vagal impairment (Porges, 2011). The question that researchers have sought
955 to answer, therefore, has been whether psychiatric disorders are characterized by reductions in HRV
956 and more recently, whether HRV alterations are present during remission. While these questions
957 have been addressed, reported findings have been contradictory. Researchers have also debated
958 whether HRV is reduced in psychiatric disorders or whether these reductions are driven by
959 medications for these conditions. We have sought to address these issues in a number of studies by
960 employing meta-analytic and other techniques, allowing us to draw conclusions from the
961 contradictory body of literature. This research on major depressive disorder (MDD) (Kemp et al.,
962 2010), anxiety disorders (Chalmers, Quintana, Abbott, & Kemp, 2014), schizophrenia (Clamor,
963 Lincoln, Thayer, & Koenig, 2016), borderline personality disorder (Koenig, Kemp, Feeling, Thayer,
964 & Kaess, 2016) and antidepressants (Kemp, Brunoni, et al., 2014a; Kemp et al., n.d.) is briefly
965 reviewed below. All these studies have demonstrated that these disorders are associated with low
966 HRV. In fact, an independent meta-analysis by colleagues (Alvares, Quintana, Hickie, & Guastella,
967 2016) has reported that HRV is reduced in all patient groups including mood, anxiety, psychosis and
968 dependent disorders (Hedges $g = -0.583$) and that findings remained highly significant for
969 medication-free patients compared to controls across all disorders. An exception to this take home
970 message is the recent systematic review published on bulimia nervosa (Peschel et al., 2016), which
971 reported increased – not decreased – HRV in this condition. This finding is discussed further below
972 in the section on theoretical conundrums & methodological limitations.

973

974 The meta-analysis on patients with MDD (Kemp et al., 2010) was conducted to determine whether
975 otherwise healthy, and unmedicated depressed patients display reductions across a variety of time-,
976 frequency- and non-linear domain measures of HRV. This was important because cardiovascular
977 disease may have led to overestimation of the association between depression and resting-state HRV
978 in prior studies. An earlier study (Licht et al., 2008) based on the large Netherlands Study of
979 Depression and Anxiety (NESDA) cohort ($N = 2,373$) had also recently concluded that lowered
980 HRV in depression was mainly driven by the effects of antidepressant medications. By contrast, our
981 meta-analysis revealed that MDD patients ($n = 673$) did display lower HRV, relative to healthy
982 controls ($n = 407$), effect sizes ranging from small (based on time- and frequency-domain HRV
983 measures; Hedges' $g = -0.3$ and -0.29 , respectively) to large (non-linear measures; Hedges' $g =$
984 1.955 , highlighting the utility of non-linear HRV measures). Depression severity was also
985 negatively correlated with HRV ($r = -0.35$, $p < 0.001$). Tricyclic antidepressants – but not other
986 classes of antidepressants – were also associated with substantial HRV reductions, findings

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987 associated with a large effect size (Hedges' $g = -1.24$). In a more recent study (Kemp et al., n.d.), the
988 effects of SSRIs have been shown to be heterogeneous, such that users of paroxetine display HRV
989 reductions relative to other users of SSRIs, while fluoxetine was the only SSRI not associated with
990 HRV reductions.

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993 The meta-analysis on anxiety disorders (Chalmers et al., 2014) was conducted on a total of 2,086
994 patients and 2,294 controls. Like the meta-analysis conducted on MDD, this study was conducted
995 because prior studies had reported inconsistent findings, again, highlighting the need for an
996 objective meta-analysis. An earlier study, again on the NESDA cohort ($N = 2,095$), had concluded
997 that while HRV was reduced in the anxiety disorders, that findings were again, primarily driven by
998 the effects of antidepressant medications. In the more recent meta-analysis (Chalmers et al., 2014),
999 anxiety disorders were characterized by lower HRV (based on HF-HRV and time-domain
1000 measures), findings associated with a small-to-moderate effect size (time-domain HRV, Hedges' $g =$
1001 -0.45 ; HF-HRV, Hedges' $g = -0.29$). Importantly, medication use and medical comorbidity did not
1002 impact on these findings. Further inspection of specific disorders indicated that patients with panic
1003 disorder ($n = 447$), post-traumatic stress disorder ($n = 192$), generalized anxiety disorder ($n = 68$) and
1004 social anxiety disorder ($n = 90$) all displayed moderate reductions in HF-HRV, relative to controls.
1005 Patients with specific phobias ($n = 61$) also displayed reductions in time-domain measures of HRV,
1006 although these findings were associated with a small effect size. Only obsessive-compulsive
1007 disorder was not associated with significant reductions in HRV, null findings that may have been
1008 due to a relatively small sample size ($n = 40$). Unfortunately, meta-analysis could not be conducted
1009 on specific treatments of anxiety disorders due to the small number of studies investigating this
1010 issue, highlighting the need for further research in this area.

1011

1012 In the largest independent cohort to date ($N = 15,105$), we reported that use of antidepressant
1013 medications is associated with robust increases in heart rate and decreases in its variability (d 's
1014 ranged from 0.37 - 0.95) (Kemp, Brunoni, et al., 2014a). However, we also observed that generalised
1015 anxiety disorder displays replicable, albeit small, reductions in vagal activity after controlling for
1016 multiple confounding variables, including medication use. This study was unique in that it
1017 capitalized on propensity score matching procedures, which have several advantages over
1018 ANCOVA and traditional regression-based techniques including reduced bias by estimating
1019 propensity scores without reference to the outcome variable (i.e. HRV) (McCaffrey et al., 2013).
1020 While it is notable that participants with depression did not display reductions in vagal activity in

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1021this analysis, this study has since been extended (Kemp, Brunoni, et al., 2014a), and new findings
1022indicate that patients with melancholia (n=40) display robust alterations in resting state heart rate
1023and its variability (measured by resting state time-, frequency- and non-linear domain measures),
1024relative to controls (n=94). These findings were associated with a moderate effect size (d 's = 0.56–
10250.58) and highlight the important impact of disorder heterogeneity.

1026

1027It is also important to realize that MDD and anxiety are frequently comorbid conditions: MDD has
1028high-comorbidities with the whole range of anxiety disorders (Goldberg & Fawcett, 2012).
1029Correlations range from 0.62 for generalized anxiety disorder, 0.52 for agoraphobia and social
1030phobia, 0.48 for panic disorder and 0.42 for obsessive compulsive disorder (Goldberg & Fawcett,
10312012). The close relationship between MDD and generalized anxiety disorder in particular, is
1032thought to relate to shared symptoms – especially negative affect – and genetic risk factors
1033(Goldberg & Fawcett, 2012). It is also relevant therefore that MDD patients with comorbid
1034generalized anxiety disorder have been shown to display the most robust reductions in HRV (Kemp,
1035Quintana, Felmingham, Matthews, & Jelinek, 2012a). These findings may relate to patients inability
1036to disengage from threat detection, even in the absence of any real threat (Kemp, Quintana,
1037Felmingham, Matthews, & Jelinek, 2012a; Thayer & Lane, 2000). This behavioral characteristic
1038may be underpinned by prolonged prefrontal inactivity, disinhibition of the central nucleus of the
1039amygdala, and activation of medullary cardioacceleratory circuits (Kemp, Quintana, Felmingham,
1040Matthews, & Jelinek, 2012a; Thayer et al., 2009).

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1042The mood and anxiety disorders themselves, are often comorbid with alcohol dependence (e.g.
1043Merikangas et al., 1998), a condition that has also been associated with a body of contradictory
1044evidence. A large study on 2,947 participants from the NESDA cohort (Boschloo et al., 2011) had
1045reported that alcohol use, but not its dependence, is associated with dysregulation of the
1046hypothalamic-pituitary-adrenal axis and the ANS. Critically however, heavy drinkers only displayed
1047an increased heart rate, but no decreases in HRV, as measured by RSA. However, the more recent
1048meta-analysis on patients with alcohol dependence (n=177) (Quintana, McGregor, Guastella, Malhi,
1049& Kemp, 2013c) observed a lowered HRV in this patient group (relative to non-dependent
1050individuals, n=216), a finding associated with a medium effect size (Hedges' g = -0.6). Importantly,
1051inclusion of the data reported by Boschloo and colleagues (Boschloo et al., 2011) did not change the
1052conclusions drawn in the meta-analysis (Quintana, McGregor, Guastella, Malhi, & Kemp, 2013c).
1053Also, findings were not dependent on comorbid psychiatric disorders. It was concluded that lowered
1054HRV in alcohol dependence may underpin some of the behavioral features of the disorder including

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1055social dysfunction (Monnot, Nixon, Lovallo, & Ross, 2001) and impulse control (Ingjaldsson,
1056Laberg, & Thayer, 2003).

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1058While alcohol dependence are associated with HRV reductions, moderate, habitual drinking (n=25)
1059– classified according to a score of between 2 and 5 on the Alcohol Use Disorder Identification Test
1060Consumption subscale (AUDIT-C) corresponding to ~1 standard drink, 5 days a week – is
1061associated with an increase in resting-state, vagal activity (HF-HRV), relative to nonhabitual
1062drinkers (n=22) ($d = 0.65$) (Quintana, Guastella, McGregor, Hickie, & Kemp, 2013a).
1063Epidemiological studies indicate that the relationship between alcohol consumption and health
1064outcomes reflects a J-shaped curve (Corrao, Bagnardi, Zambon, & La Vecchia, 2004; Elkind et al.,
10652006; Hvidtfeldt et al., 2010; Stampfer, Colditz, Willett, Speizer, & Hennekens, 1988): moderate
1066alcohol consumption confers a protective effect, relative to abstinence, while heavy consumption
1067and dependence is associated with poorer health. For example, a meta-analysis on 156 studies of 15
1068diseases (N=116,702) reported a minimum risk ratio 0.80 for coronary heart disease at 20 g/day
1069indicating a significant protective effect, which was observed up to 72 g/day, while increased risk
1070was obtained from 89 g/day (RR > 1.05) (Corrao et al., 2004). We (Quintana, Guastella, McGregor,
1071Hickie, & Kemp, 2013a) have previously proposed that resting (tonic) vagal activity may provide a
1072candidate psychophysiological marker for the findings reported in the epidemiological literature.

1073

1074Our meta-analysis on schizophrenia (Clamor et al., 2016) was conducted to determine the
1075robustness and size of the effect that had been reported in prior studies. While HRV decreases had
1076been reported, there was considerable heterogeneity in the HRV indices that had been selected, the
1077type of participants recruited in studies and in the results that had been reported. A meta-analysis
1078was conducted on large samples of participants and a large effect size across studies was confirmed
1079for both RMSSD (N= 2,485; Hedges' $g = -0.91$) and HF-HRV (N= 3,055; Hedges' $g = -0.98$), and
1080the effect persisted even when studies that could have been impacted on by bias were excluded from
1081analysis. HRV alterations were also examined across different sub-groups of the disorder, including
1082first-episode, chronic, acute inpatient, stable outpatient as well as medicated and unmedicated
1083participants, emphasizing the robustness of the results. This study concluded that low HRV in
1084schizophrenia may actually reflect an endophenotype of the disorder. HRV reflects prefrontal
1085cognitive function, and schizophrenia displays complex executive dysfunction (Neill & Rossell,
10862013). HRV also reflects capacity for emotion perception and its regulation, and schizophrenia also
1087displays difficulties in emotion regulation (Lincoln, Hartmann, Köther, & Moritz, 2015). Finally,
1088brain regions in which activity has been associated with HRV such as anterior cingulate cortex and

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1089medial prefrontal cortex, have also been implicated in the development of schizophrenia (Shepherd,
1090Laurens, Matheson, Carr, & Green, 2012). While the large effect size associated with the finding is
1091striking, and this effect is greater than that observed for the mood and anxiety disorders, direct
1092comparisons across disorders are rare and inconclusive (e.g. Moon, Lee, Kim, & Hwang, 2013),
1093highlighting an important area for future research.

1094

1095As for schizophrenia, borderline personality disorder (BPD) is also associated with emotion
1096dysregulation and is characterised by high rates of comorbidity with mood and anxiety disorders,
1097and substance abuse disorders. However, only two of the 5 studies suitable for meta-analysis
1098actually reported statistically significant differences between BPD participants and controls. The
1099meta-analysis on BPD (Koenig et al., 2016) therefore sought to quantify the evidence for alterations
1100in resting state HRV, relative to healthy controls (N=200). A reduction in resting-state HRV was
1101confirmed, a finding associated with a medium effect size (Hedges' $g = -0.59$), highlighting the
1102utility of meta-analysis over individual studies, which often lack statistical power. This meta-
1103analysis concluded that low HRV may reflect an important trait characteristic of BPD, underpinning
1104difficulties in emotion regulation and impulsivity.

1105

1106In addition to HRV reductions during the presence of the disorder, we note that studies have also
1107observed HRV reductions during euthymia (Braeken et al., 2013; Brunoni et al., 2013; H. A. Chang
1108et al., 2013b). These findings suggest that vagal impairment may actually persist despite successful
1109treatment, perhaps providing a psychophysiological mechanism for the observation that previously
1110depressed individuals are more vulnerable to future episodes of depression, a phenomenon known
1111as 'kindling' (Post, 1992). While it is possible that these persistent reductions in HRV relate to the
1112impact of medications including antidepressants (Kemp et al., 2010; Kemp, Brunoni, et al., 2014a;
1113Licht, de Geus, van Dyck, & Penninx, 2010) and medications with anticholinergic effects (often
1114prescribed for hypertension and cardiovascular disease) we recently demonstrated that unmedicated
1115women with a history of – but not current – anxiety disorders display decreased HRV (RMSSD $d =$
11160.58; HF-HRV $d = 0.72$) (Braeken et al., 2013). Strikingly, we also observed (Braeken et al., 2013)
1117that 2-4 month old offspring of pregnant women with a past history – but not current – anxiety also
1118display HRV reductions (RMSSD $d = 0.63$; HF-HRV $d = 0.63$). These decreases in HRV at 2-4
1119months of age also predicted fearful behaviour at 9-10 months of age, pointing to possible
1120underlying mechanisms of future psychopathology. In another study (Brunoni et al., 2013) HRV did
1121not change following treatment with either a non-pharmacological (transcranial direct current
1122stimulation) or pharmacological (sertraline) intervention, nor did HRV increase with clinical

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1123response to either treatment. Another study on an unmedicated, physically healthy sample (H. A.
1124Chang et al., 2013b) observed that while HRV resolved in patients with fully remitted MDD,
1125autonomic dysregulation was still observed in those remitted patients with a history of suicidal
1126ideation. Further study on the potential of other non-pharmacological therapies (e.g. psychological
1127therapies, exercise, meditation and HRVB) to normalize vagal impairment will likely have major
1128public health significance.

1129

1130In addition to health behaviours such as exercise and meditation (see previous sections), it is worth
1131noting research interest in applying HRV biofeedback (or HRVB) in the treatment of a variety of
1132psychiatric disorders including depression, anxiety and PTSD (Gevirtz, 2013; Lehrer & Gevirtz,
11332014). While adults generally breathe at 9 to 24 breaths per minute (or 0.15 and 0.4Hz, the
1134frequency range of HF-HRV), HRVB involves slowing breathing rates to approximately 6 breaths
1135per minute with a focus on prolongation of the outbreath. When people breathe normally, heart rate
1136is partially out of phase with respiration such that heart rate increases (decreases) tend to follow
1137inhalation (exhalation) at the mid-breath point. It has been speculated that this out-of-phase
1138relationship allows the greatest degree of cardiorespiratory flexibility to the organism (Lehrer &
1139Gevirtz, 2014). However, when people slow their breathing to ~6 breaths per minute (~0.1Hz)
1140(increasing power in LF-HRV) heart rate begins to oscillate with breathing at a 0° phase
1141relationship, such that heart rate starts increasing at the beginning of inhalation and starts decreasing
1142as exhalation begins (Lehrer & Gevirtz, 2014). When people breathe at this rate they are said to be
1143“exercising their baroreflex” leading to more efficient gas exchange and oxygen saturation (Shaffer
1144et al., 2014). A single-session of slow breathing and HRV biofeedback has been shown to enhance
1145HRV and decrease self-reported anxiety in anxious musicians during stressful performance (Wells,
1146Outhred, Heathers, Quintana, & Kemp, 2012). Again, vagal afferent pathways may explain some of
1147the observed beneficial central effects of HRVB (Lehrer & Gevirtz, 2014) including enhanced
1148attention and alertness, and reduced anxiety. While it is unlikely that HRVB will be a magic bullet
1149that many are after in psychiatry, it’s utility as a secondary and complimentary option remains to be
1150systematically examined in well-controlled trials.

1151

1152**Summary**

1153These findings highlight that low HRV is displayed in a wide range of psychiatric disorders and
1154have led us to propose HF-HRV as an autonomic, transdiagnostic biomarker of mental illness
1155(Beauchaine & Thayer, 2015). This impairment in vagal function may contribute to some of the
1156characteristic features (e.g. emotion dysregulation) commonly observed across these disorders.

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1157Critically, vagal impairment often does not improve with amelioration of symptoms, and this
1158impairment may even impact on the offspring of mothers with prior psychiatric illness (Braeken et
1159al., 2013), highlighting the need for further studies to identify treatment options to normalize vagal
1160function in these populations. The long-term consequences of reduced vagal function on physical
1161health are the issues we turn our attention to next.

1162

1163 **Vagal Function and Physical Health**

1164

1165Research has highlighted an intimate relationship between psychological and physical wellbeing,
1166and vagal function may provide a structural link (see Kemp & Quintana, 2013 for review). Meta-
1167analysis on 35 studies investigating mortality in initially healthy populations (Chida & Steptoe,
11682008) reported that positive psychological wellbeing is associated with reduced mortality in healthy
1169individuals. Stronger protective effects were observed for studies of initially healthy populations
1170with follow-ups of up to 10 years. Analyses of different causes of death revealed that wellbeing was
1171associated with reduced all-cause mortality (19% reduction in hazard ratio) and cardiovascular
1172mortality (29% reduction). Importantly, these findings are based on multivariate models with
1173appropriate adjustment for potential confounding factors. By contrast, a study on more than 65,000
1174people from the general population who were free from cardiovascular disease and cancer at
1175baseline reported that psychological distress increases risk of mortality in a dose-response pattern
1176by up to 94% over 8 years (Russ et al., 2012). Again findings remained highly significant even after
1177controlling for important behavioural and lifestyle factors. Finally, a recently published meta-review
1178on 20 different mental disorders in over 1.7 million patients reported that all disorders have an
1179increased risk of all-cause mortality, relative to the general population. Strikingly, all major mental
1180disorders were associated with reductions in life expectancy (7-24 years), which was similar to or
1181greater than the effects of heavy smoking (8-10 years) (Chesney, Goodwin, & Fazel, 2014).

1182

1183We and others have previously reviewed the literature on the role of vagal function in morbidity and
1184mortality (Kemp & Quintana, 2013; Thayer, Yamamoto, & Brosschot, 2010c), and have suggested
1185that chronic vagal impairment may have a ‘wear and tear’ effect on the human body (Verkuil,
1186Brosschot, Gebhardt, & Thayer, 2010). These effects include increases in the electrical instability of
1187the heart, platelet aggregability, coronary vasoconstriction and left-ventricular wall stress (P. J.
1188Schwartz & Priori, 1990). A prospective study on 1933 participants aged 18 to 65 years from the
1189Netherlands Study of Depression and Anxiety (NESDA) study, reported that ANS dysregulation
1190predicts development of the metabolic syndrome (Licht, de Geus, & Penninx, 2013). ANS measures

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1191 included heart rate, RSA, pre-ejection period (or PEP, a marker of noradrenergic ionotropic drive to
1192 the left ventricle such that shortened PEP reflects increases in sympathetic activity), cardiac
1193 autonomic balance (CAB) and cardiac autonomic regulation (CAR). The CAB and CAR indices
1194 provide two useful measures of autonomic balance (Berntson, Norman, Hawkley, & Cacioppo,
1195 2008). High values on CAB reflect a favourable cardiac pattern of low sympathetic (indexed by
1196 PEP) and high vagal (RSA) cardiac activity, while low (high) values on CAR reflect coinhibition
1197 (coactivation) of the two cardiac branches. This study (Licht et al., 2013) defined metabolic
1198 syndrome by the Adult Treatment Panel III criteria (Grundey et al., 2005), which included high waist
1199 circumference, serum triglycerides, blood pressure, serum glucose, and low high-density lipoprotein
1200 (HDL) cholesterol. Baseline quartiles of heart rate, PEP, CAB were associated with new onset of the
1201 metabolic syndrome among those without metabolic syndrome at baseline. Higher heart rate was
1202 associated with an increase in the odds for new onset of metabolic syndrome (OR=1.97), while
1203 higher PEP and CAB were associated with a decrease in the odds for new onset (OR = 0.46 and OR
1204 = 0.57, respectively). How might high CAB reduce odds for metabolic syndrome? Vagal function is
1205 known to play an important role in regulating the inflammatory reflex (Tracey & Pavlov, 2012), a
1206 neural mechanism involved in metabolic homeostasis and control of innate immune responses. In
1207 this regard, high CAB may reflect a healthy anti-inflammatory reflex (see Kemp & Quintana, 2013;
1208 Tracey & Pavlov, 2012 for reviews), contributing to better regulation of proinflammatory cytokine
1209 activity and protecting against other metabolic complications (Donath & Shoelson, 2011;
1210 Hotamisligil, 2006). Decreased HRV has been shown to precede elevated levels of inflammatory
1211 markers (Jarczok et al., 2014), thus, interventions that increase HRV may have positive effects on
1212 diseases of inflammation and metabolic syndrome via downstream pathways including the SNS.

1213

1214 Short-term, resting and ambulatory measures of HRV decrease with increasing age (Agelink et al.,
1215 2001; Jennings & Mack, 1984; Yeragani et al., 1997), and age is associated with increasing
1216 morbidity and mortality, highlighting age as an important confounding variable in studies exploring
1217 associations between vagal function, morbidity and mortality. Cross-sectional research on 344
1218 healthy participants ranging from 10 to 99 years of age (Zulfiqar, Jurivich, Gao, & Singer, 2010)
1219 highlighted that HRV (RMSSD, pNN50) – extracted from 24-hour ambulatory Holter recordings –
1220 decreases rapidly from the second to fifth decades ($r = -0.58$), this decrease then reaches a nadir in
1221 the 8th decade, after which a significant, progressive increase to higher levels is observed. At the
1222 nadir, RMSSD had decreased 64% and pNN50 88% from the second-decade baseline values, while
1223 the tenth decade was characterised by increases in RMSSD and pNN50 of 58% and 233%
1224 respectively, characteristic of values obtained during the fifth-decade. It is possible that this latter

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1225increase reflects a survival bias, such that older participants with low HRV may have already died
1226before the study was conducted, leading to an artificial increase in HRV following the 8th decade.
1227Even so, findings still highlight the tight connection between vagal function, ageing and longevity.
1228The authors themselves concluded that persistently high HRV in the elderly is predictive of
1229longevity.

1230

1231Research has typically focused on populations with current cardiovascular disease, and examined
1232the capacity for HRV to predict future adverse events (see Carney & Freedland, 2009 for a review)
1233(see also Bigger et al., 1988; Huikuri & Mahaux, 2003; Karp et al., 2009). Findings indicate that
1234HRV accounts for a substantial part of the risk associated with depression in CHD. For example, a
1235study on 311 depressed patients with a recent acute myocardial infarction recruited for the
1236Enhancing Recovery in Coronary Heart Disease (ENRICHD) study (Carney et al., 2005), reported
1237that depressed patients remained at a higher risk for all-cause mortality over a 30-month follow-up
1238period (hazard ratio: 2.8) after adjusting for potential confounders. The authors reported that
1239reduced very low frequency HRV based on 24-hour ambulatory Holter recordings accounted for
1240one-quarter of the mortality risk relating to depression. Another prospective study (Carpeggiani,
12412005) that followed 246 patients after myocardial infarction reported that personality traits
1242including low emotional insensitivity and insecurity, as well as reduced HF-HRV – measured using
124324-h Holter monitoring – predicted increased risk for cardiac mortality (relative risk = 4.18 and
12442.76, respectively) up to 8-years following initial event. Low emotional sensitivity reflects social
1245inhibition and an inability to express emotion, a characteristic that may be associated with reduced
1246HRV itself (as discussed above). This restricted capacity to express emotion may lead to chronic
1247distress, which will further contribute to impairment in vagal function. Importantly, participants in
1248this study did not have a history of psychiatric illness, nor were they on psychotropic medications.

1249

1250A study in mice (Norman et al., 2012) sought to better understand what mechanisms might underpin
1251the increase in morbidity and mortality following myocardial infarction. This study randomly
1252assigned animals to two experimental groups: normothermic cardiac arrest (n=12) or hypothermic
1253cardiac arrest (as a control group, n=10). Cardiac arrest was induced through injection of potassium
1254chloride via a jugular catheter, and this was followed by injection of epinephrine and chest
1255compressions. The heads of controls were maintained at 27°C to prevent neurological damage. HF-
1256HRV was observed to decrease rapidly 24h after experimentally induced cardiac arrest, and these
1257decreases were correlated with neuronal damage and microglial activation in hippocampus by day
12587. This study provides important clues in regards to the physiological consequences of cardiac arrest

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1259resulting from cessation of blood flow to the brain (global cerebral ischemia), and suggests that low
1260HRV may provide a marker of subsequent brain damage. The authors note that the hippocampus is
1261one of the more susceptible regions of the brain to ischemic damage, that this region directly
1262innervates structures within the CAN, and that stimulation of this region is associated with
1263decreases in heart and respiration rate. While the authors acknowledge that the study was not able to
1264determine a causal relationship between neuroinflammation and vagal function, their findings
1265indicate that vagal function following cardiac arrest may provide an index of susceptibility to
1266neuronal damage.

1267

1268Resting-state heart rate has been shown to be an independent predictor of cardiovascular and all-
1269cause mortality in men and women with and without a diagnosis of cardiovascular disease at initial
1270assessment (see Fox et al., 2007 for review). More recent studies (e.g. Cooney et al., 2010; Saxena
1271et al., 2013) on large samples have only served to reinforce the conclusions drawn in this earlier
1272review. The heart is under tonic inhibitory control by the SNS during the resting state. Resting state
1273heart rate and HRV therefore provide surrogate markers of vagally mediated cardiac activity,
1274although it is noted that measures of HRV and the high-frequency component in particular are more
1275pure indicators of vagal activity than heart rate (Saul, 1990). A study on 21,853 participants from
1276the National FINRISK cohort reported a causal relationship between resting heart rate and incident
1277cardiovascular disease over a 6 to 27 year follow-up period that was independent of other risk
1278factors (Cooney et al., 2010). Hazard ratios for cardiovascular disease for each 15 beats/min
1279increase in resting heart rate were 1.24 in men and 1.32 in women. Strikingly, resting heart rate >90
1280beats/min, relative to <60 beats/min, are associated with approximately 2-fold increased risk of
1281CVD mortality in men and a 3-fold increased risk in women, findings that are similar in magnitude
1282to the risk associated with smoking. The possibility of reverse causality was ameliorated in this
1283study by replicating findings after excluding individuals with comorbidities and events occurring
1284within the first 2 years of observation. A stronger effect was also observed on fatal events leading
1285the authors to suggest that proarrhythmogenicity may be one of the mechanisms underpinning the
1286deleterious effects of increased resting heart rate. Another recent study on 53,322 patients receiving
1287a medical examination reported that those with a resting heart rate of ≥ 80 beats/min had a greater
1288risk for cardiovascular disease (hazard ratio = 1.38) and all-cause mortality (hazard ratio = 1.51),
1289than those with a resting heart rate of less than 60 beats/min over an average follow-up period of 15
1290years (Saxena et al., 2013). The hazard ratios were even higher when combining resting heart rate
1291with a measure of cardiorespiratory fitness. Unfit individuals with a high resting heart rate (≥ 80
1292beats/min) had hazard ratios of 2.32 and 2.21 for cardiovascular disease and all-cause mortality,

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1293respectively. Importantly, these findings were obtained after adjusting models for a host of
1294potentially confounding factors.

1295

1296Similarly, meta-analysis has reported that HRV – based on a variety of measures extracted from
1297short- and long-term recordings – predicts first cardiovascular event in individuals without known
1298cardiovascular disease over a period of 3.5 to 15 years (mean follow-up duration of included
1299studies) (Hillebrand et al., 2013). Cardiovascular endpoints included hospitalization for angina
1300pectoris, myocardial infarction, congestive heart failure, arterial peripheral vascular disease,
1301coronary revascularization, stroke and cardiovascular death. This study was based on eight studies
1302with a total of 21,988 participants without known cardiovascular disease at baseline reported pooled
1303relative risks for a first cardiovascular event ranging from 1.35, 1.45 and 1.32 for standard deviation
1304of the normalized N–N interval (SDNN), LF-HRV or HF-HRV measures respectively. This study
1305also reported that relative risk of incident CVD of 1.50 and 0.67 for the 10th and 90th HRV (SDNN)
1306percentiles relative to the 50th percentile, respectively. These findings were based on a variety of
1307study populations including the Framingham Heart Study (USA, N=2501), the Atherosclerosis Risk
1308in Community Study (USA, N=11,647), Rotterdam Study (the Netherlands, N=5,272), as well as
1309other smaller cohort studies. The authors concluded that low HRV is associated with a 32-45%
1310increased risk of cardiovascular event, and that an increase of 1% on SDNN in particular, results in
1311~1% lower risk of fatal or non-fatal CVD at follow-up. Two possible mechanisms were proposed
1312including autonomic imbalance activating inflammation by influencing bone marrow and the
1313lymphoreticular system. The other suggested mechanism was that individuals with low HRV
1314already suffer from subclinical or silent CVD. Here we suggest a third and more likely possibility of
1315bidirectional relationship between disease and vagal function such that vagal impairment leads to
1316dysregulation of immune system triggering downstream atherosclerotic processes as described by
1317Tracey and colleagues (Huston & Tracey, 2010; Tracey, 2002; 2007; Tracey & Pavlov, 2012), as
1318well as adverse effects of the disease process itself on HRV.

1319

1320**Summary**

1321In summary, studies have highlighted a key role for vagal function in longevity and its impairment
1322as a causal factor in morbidity and mortality. We highlight two major findings: (1) vagal function
1323has important long-term consequences for future health and wellbeing after addressing multiple
1324confounding factors, and (2) impairment in vagal function predicts cardiovascular and all-cause
1325mortality in those with *and* without cardiovascular disease at baseline. We now synthesise the body

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1326of literature reviewed above, and present a model that attempts to bridge the gap from everyday
1327psychological moments to mortality.

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1329

A Synthesis and Model

1330

1331Here we propose an extended NIM that we label as Neurovisceral Integration Across a Continuum
1332of Time (or NIACT) (see Fig 3). The vagus nerve may be considered the most important nerve in
1333the human body, not only supporting everyday psychological moments and flexible responding to
1334environmental change (as we have reviewed above), but also in playing a major regulatory role over
1335a variety of allostatic systems thereby contributing to increases or decreases in risk for future
1336morbidity and mortality. Our model provides a framework through which vagal function can be
1337considered a critical, structural link between everyday psychological moments and mortality. An
1338important distinction is made between phasic and tonic measures of vagal function. Phasic changes
1339during an activity or task reflect ongoing, moment-to-moment psychophysiological adaptations to
1340environmental challenge, while resting-state measures of vagal function index fundamental
1341psychophysiological resources that support psychological flexibility and health that will both affect
1342and be affected by the cascade of physiological processes subsequently impacting on individual risk
1343for morbidity and mortality.

1344

1345INSERT FIGURE 3 ABOUT HERE

1346

1347Our model explicitly recognises bidirectional relationships between vagal function and
1348psychological moments, which over time will contribute to physical disease (wellbeing) and
1349mortality (longevity). Our model also draws on evidence (Kok et al., 2013; Kok & Fredrickson,
13502010) that highlights mutual causation between psychological moments and vagal function, such
1351that increases (decreases) in function will reciprocally and prospectively predict each other in an
1352upward (downward) spiral of reciprocal causality. Vagal nerve outflow and connections with other
1353cranial nerves will contribute to the capacity for social engagement, impairment on which is a core
1354characteristic of the psychiatric disorders (Porges, 2011; Quintana, Kemp, Alvares, & Guastella,
13552013b). The mood and anxiety disorders without cardiovascular disease display impaired vagal
1356function (Kemp et al., 2010; Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012a), which
1357may subsequently trigger the inflammatory cascade (Kiecolt-Glaser et al., 2002) and allostatic load
1358(Danese & McEwen, 2012; McEwen, 1998) leading to morbidity and mortality. On the other hand,

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1359physical disease may also contribute to the development of psychiatric illness. Recent population-
1360based, prospective cohort studies – on 3.56 million people with more than 77 million person-years
1361of follow-up (Benros et al., 2011; 2013) – show for example, that hospitalisation for autoimmune
1362diseases and severe infection increase the risk for schizophrenia and mood disorders in a dose-
1363response relationship.

1364

1365Our model has a variety of implications for scientific endeavour and public health outcomes. For
1366instance, heart rate monitoring may provide a useful – and relatively simple – means to predict and
1367promote longevity especially in the elderly and other at-risk populations. While age decreases vagal
1368function, there are many interventions that may be applied to combat such decreases including a
1369variety of health behaviours, meditation, and positive psychological interventions. Improvements in
1370technology provide many opportunities for individuals to track their own vagal function without
1371need for health care involvement. Health behaviours including physical activity, dietary changes,
1372and reducing alcohol and tobacco consumption directly impact on vagal function and provide
1373simple, effective interventions to improve public health. Research has highlighted the beneficial
1374effects of positive psychological interventions on risk for future cardiac outcomes (Boehm &
1375Kubzansky, 2012; Dubois et al., 2012; Sin & Lyubomirsky, 2009), and these effects may persist
1376over and above addressing chronic negative emotions. Importantly, there appears to be a
1377bidirectional relationship between emotion and vagal function, such that one predicts the other in an
1378upward (or downward?) spiral of reciprocal causality (Kok et al., 2013; Kok & Fredrickson, 2010).
1379The possibility of mutual causation between an emotion and vagal function is a powerful idea: by
1380altering a psychological moment, we have an opportunity to harness an upward spiral of positive
1381mood, resilience and longevity.

1382

1383**Summary**

1384In summary, we characterise vagal function as a critical, missing link that may help to bridge the
1385gap between everyday psychological functioning and mortality. This proposal is founded on a series
1386of empirically supported relationships, suggesting that vagal function may provide an appropriate
1387target for improved health and wellbeing. We now turn our attention to some of limitations
1388associated with prior research and provide a number of recommendations for future research.

1389

1390 **Theoretical Conundrums & Methodological Limitations**

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1392The body of research reviewed above provides considerable evidence on which our proposal is
1393based: that vagal function may provide the missing structural link between everyday psychological
1394moments and mortality. People's reactions to everyday moments both affect and are affected by the
1395vagus in ways that have long-term effects on mortality. However, the literature is also characterised
1396by a variety of theoretical conundrums and contradictory findings. We briefly review and comment
1397on some examples below, an effort we hope will motivate and inspire future studies to further
1398explore some of the issues raised, bearing in mind the various methodological limitations noted.

1399

1400Firstly, a meta-analysis (N= 11,162) has demonstrated robust ethnicity effects on HRV – including
1401short-term measures of HF-HRV, RSA and RMSSD – demonstrating that African Americans have
1402higher HRV than individuals with a white European background (Hedges $g = 0.93$) (Hill et al.,
14032015). These findings were observed even after consideration of several covariates including health
1404status, medication use, and subgroup stratification by sex and age. Curiously, African Americans
1405also have higher mortality rates from coronary heart disease and stroke (Keenan & Shaw, 2011), a
1406surprising finding considering that increased HRV is usually associated with reduced, not increased
1407risk for cardiovascular disease, a phenomenon we (Hill et al., 2015) have labeled as a
1408cardiovascular 'conundrum'.

1409

1410Secondly, research on eating disorders – and a systematic review on bulimia nervosa in particular –
1411has observed increased – not decreased – resting state vagally-mediated HRV, as well as an
1412impaired stress-response. Bulimia nervosa is a serious mental illness characterized by recurrent
1413episodes of binge-eating and subsequent compensating behaviours such as self-induced vomiting
1414and over-exercising. We described several behavioural factors that might contribute to heightened
1415HRV in this disorder including compensation for a lack of energy provided by nutrition, over-
1416exercising, and self-induced vomiting leading to supra-threshold vagal activation. By contrast, a
1417review on anorexia nervosa (Mazurak, Enck, Muth, Teufel, & Zipfel, 2010) concluded that the body
1418of literature has been contradictory and that these contradictory findings may be a result of
1419methodological limitations including age, BMI, illness duration, and comorbidity with other
1420psychiatric disorders including depression and anxiety. Contradictory findings highlight the need for
1421meta-analytic studies, in addition to further research on larger samples that better control for
1422confounding variables, and harness the rigour of repeated measures and longitudinal designs. Like
1423that for anorexia nervosa, it is noted that the systematic review on bulimia nervosa was not a meta-
1424analysis.

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1426Thirdly, other lines of evidence indicate that high levels of vagal function may be observed in
1427individuals at risk of mania (Gruber, Johnson, Oveis, & Keltner, 2008) and in bipolar disorder
1428(Gruber, Harvey, & Purcell, 2011). Participants characterised by high – relative to low risk – for
1429mania, according to the Hypomanic Personality Scale (HPS) (Eckblad & Chapman, 1986), display
1430elevated positive emotion and tonic vagal function ($d = 0.53$) at rest (based on a 90-sec pre-film
1431baseline when participants were completing questionnaires), as well as during presentation of
1432positive, negative and neutral films ($d = 0.47$) (Gruber et al., 2008). Although this study was based
1433on young adults ($N=90$), the HPS captures elevations in positive mood states and high-scorers on
1434this measure have been shown to overlap with bipolar patients. Another study by these authors
1435reported that patients with bipolar disorder ($n=23$) display smaller decreases in RSA – as
1436determined by the peak-valley method – during emotion-eliciting films, compared to non-clinical
1437controls ($n=24$) ($d = 0.61$) (Gruber et al., 2011). Interestingly, this study further reported that mean
1438RSA levels (prior to computing change scores) were higher for bipolar patients compared to
1439controls. Further research is needed on bipolar disorder, including investigating the impact of
1440different phases of the illness within patients and in comparisons with other diagnostic groups, as
1441well as meta-analysis, which may help to clarify the impact of this disorder on vagal function.

1442

1443In addition to potential methodological limitations, these contradictory findings highlight a need for
1444further research to better understand the moderating and mediating mechanisms underpinning, not
1445only chronic alterations in vagal function, but also in the downstream causal pathways leading to
1446increased morbidity and mortality in the context of established risk markers such as hypertension,
1447diabetes, abnormal cholesterol, and modifiable factors including smoking, physical activity, and
1448obesity. Research methodologists argue that “we better understand some phenomenon when we can
1449answer not only whether X affects Y, but also how X exerts its effect on Y, and when X affects Y
1450and when it does not...” (Hayes, 2013) In this regard, “the how question relates to the underlying
1451psychological, cognitive, or biological process that causally links X to Y, whereas the “when”
1452question pertains to the boundary conditions of the causal association...” (Hayes, 2013)
1453Researchers need to move beyond questions like “is there an effect?” to questions such as “when do
1454effects appear?” (moderation), “how do effects arise?” (mediation), and “how strong are these
1455effects?” (effect size) (Cumming, 2012; Hayes, 2013). In doing so, researchers will gain better
1456understanding of the causal pathways involved and clarify whether, how and when these effects
1457(HRV reductions) lead to morbidity and mortality. This approach would also provide an ideal
1458method of testing the model we propose here, determining whether vagal function provides a
1459structural link between psychological moments and mortality.

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1461 Summary

1462 In summary, while the extant research provides a solid foundation on which we propose a key role
1463 for vagal function in the pathway from psychological moments to mortality, studies have also been
1464 characterised by a variety of limitations, contradictory findings and interpretative issues,
1465 highlighting a need for continued study to further understand the relationship between everyday
1466 psychological moments and mortality. Further research is especially needed on how (mediation) and
1467 when (moderation) vagal function impacts on downstream pathways. While studies have typically
1468 emphasised the direct effects of downstream processes – such as insulin resistance and
1469 inflammatory processes – on cardiac function, research has only recently begun to account for the
1470 central effects on autonomic cardiovascular control (Harrison, Cooper, Voon, Miles, & Critchley,
1471 2013; Ryan, Sheu, Verstynen, Onyewuenyi, & Gianaros, 2013).

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Conclusions

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1475 Here we propose that the function of the vagus nerve provides an critical structural link between
1476 everyday psychological moments and mortality, a proposal we label as Neurovisceral Integration
1477 Across a Continuum of Time (or NIACT). This proposal has important implications for the study of
1478 (1) emotion and cognition, including the need for experimental studies incorporating additional
1479 measures of PNS and SNS function to better understand brain-body linkage, (2) psychiatric
1480 disorders, including the need to conceptualise these conditions as ‘embodied’ disturbances, rather
1481 than brain disorders, (3) treatments for psychiatric and physical illness, including the mechanisms
1482 through which they may mediate their effects, and (4) morbidity and mortality from a host of
1483 conditions, including the need for path modelling in longitudinal epidemiological studies exploring
1484 the impact of vagal function over and above established risk markers. We have synthesised and
1485 integrated the exciting research that is being conducted at the intersection of psychology, psychiatry
1486 and epidemiology. In conclusion, we argue that there is a critical need for more basic and applied
1487 research to better understand neurovisceral integration between brain and body function especially
1488 over the continuum of time. This research may have important theoretical and public health
1489 significance including a better understanding of the relationship between everyday psychological
1490 moments and mortality.

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1493

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2182 **Table 1: Summary of common HRV parameters and their interpretation.**

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Measure	Units	Interpretation
Time Domain		
191 MeanRR	ms	Measures of variance calculated on NN intervals (cleaned R-R time-series) to yield (milliseconds, ms). The mean of NN intervals; the longer the NN interval, the slower the heart rate (ms RR interval, the faster the heart rate (less HRV). Higher resting heart rate and lower compromised physiological state.
SDNN	ms	The standard deviation of NN intervals reflects all cyclic components responsible for recording. 24-hour recordings reflect circadian influences and total HRV, such that while lower values are associated with increased risk of mortality, especially in patients.
RMSSD	ms	Square root of the mean squared differences between successive RR intervals. This measure of HRV and reflects beat-to-beat changes mediated by the SNS. RMSSD is less affected than for the HF component.
pNN50	%	NN50 divided by the total number of RR intervals. Provides information about the fluctuations in sinus rhythm. May be less sensitive to group differences than other measures.
RSA		Respiratory sinus arrhythmia combines heart rate with respiration data, and reflects changes associated with respiration. RSA can be quantified using spectral analysis, time-domain application of a band-pass filter, so units of measurement can vary.
Frequency Domain		
High Frequency (HF)		Variance in heart rate is partitioned into frequency spectra using various approaches: transform (FFT) and autoregressive modelling techniques. HF corresponds to heart rate variations in the respiratory cycle (0.15 and 0.40 Hz). Higher values. Total vagal blockade eliminates oscillations in this frequency range.
HF-HRV(n.u.)	n.u.	HF [ms ²]/(total power [ms ²] – VLF [ms ²]). This measure minimizes the effects of overall power.
HF-HRV(ms ²)	ms ²	normalised HF can be driven either by increases in overall HF power or by decreases. Reflects parasympathetic activity, although dependent on total power. Total power (e.g. tachycardia) and increased with vagal activation, highlighting the importance of these results.
LF-HRV		LF may also be presented in normalised units [nu] and absolute power [ms ²]. Interference (0.04–0.15 Hz) is controversial and depends on the recording condition in which diaphragmatic sympathetic and baroreflex mechanisms.
192 Non-Linear		Non-linear measures assess qualitative properties rather than magnitude of heart rate variability.
193 The Poincaré plot		more sensitive to group differences, however, the physiological basis of these measures is less clear. A geometrical technique that involves fitting an ellipse to the shape of the N-N intervals.
SD1	ms ²	indices: SD1, SD2, and SD1/SD2. The minor axis of the Poincaré plot ellipse is a measure of rapid changes in the NN intervals.

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Figure Captions:

Fig 1. Visualisation of major characteristics, core components and associated behaviours described in NIM and PVT that contribute to a psychological moment. Increases in activity (black arrows) – indexed by increased phasic HRV – reflect increased inhibitory control over cardioacceleratory circuits facilitating social engagement and emotion regulation. Decreases in phasic activity (grey arrows) reflect disinhibition of the central nucleus of the amygdala and cardioacceleratory circuitry facilitating the stress response and behavioural withdrawal. The arrows represent both efferent projections from the CAN, which contribute to alterations in phasic vagal activity and related behavioural responses, as well as afferent feedback from peripheral end organs allowing for effective regulation of ongoing processing. These bidirectional pathways from and to the CAN provide a psychophysiological framework for reciprocal causality in which positive and negative emotions reciprocally and prospectively contribute to alterations in vagal function (i.e. mutual causation). Afferent projections also provide a theoretical basis through which many behavioural interventions such as massage, exercise, meditation, yoga and HRV biofeedback may be understood.

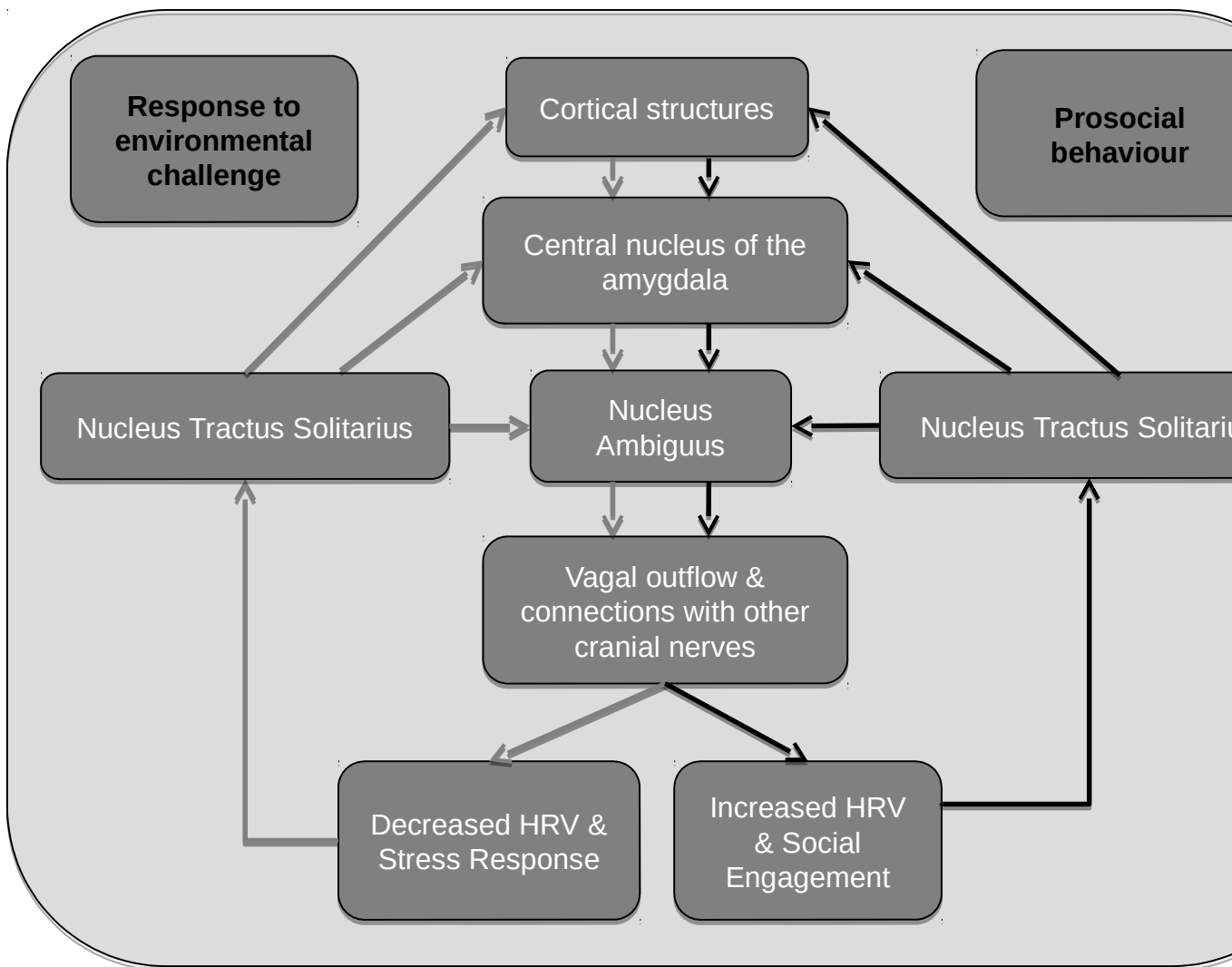
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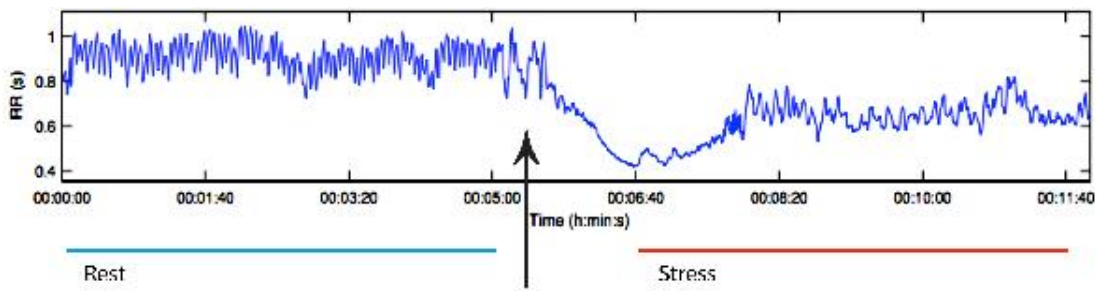
Fig 2: Example of a participant's RR-interval trace as graphed in Kubios software. Higher values on the vertical RR axis indicate slower heart rate, and variability in the trace is indicative of HRV. During rest, heart rate is characterised by slower heart rate and a high level of HRV. The stress task involving completion of the serial 13's task in combination with social pressure led to an increase in heart rate and reductions in HRV. Interestingly, heart rate increases and HRV is completely ameliorated even before the task is begun; that is, as soon as the participant is informed about the task they will shortly commence, noticeable changes arise in the trace.

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Fig 3. Neurovisceral Integration Across a Continuum of Time (NIACT) characterising the link between psychological moments to mortality: the extent of neurovisceral integration is dependent on vagal functioning and underpins experience of psychological moments (Fig 1). Impaired vagal function leads to psychophysiological rigidity, dysregulation of allostatic processes, psychiatric illness, disease and mortality. By contrast, a properly functioning vagus is associated with psychophysiological flexibility, improved control over allostasis, resilience, wellbeing and longevity. The model highlights mutual causation (bidirectional associations) between vagal nerve function, psychological moments, psychiatric illness (resilience) and disease (wellbeing).

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Task instructions for the serial 13's task

