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

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Highlights

- HRV is a psychophysiological marker of vagal function
- Everyday psychological moments both affect and are affected by the vagus
- The vagus plays a critical regulatory role over tightly integrated allostatic systems
- Changes in vagal function may provide an initial 'spark' that initiates a cascade of downstream effects
- In this way, the vagus may provide a structural link connecting moments to mortality

Abstract

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

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

Introduction

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

The 1990's was designated as 'the decade of the brain' and, more recently, Thomas Insel has proposed that mental disorders now be considered 'brain disorders' (Insel, 2013). Insel's position is that changes in the brain associated with psychiatric illness occur much earlier than observable symptoms. Waiting for observable symptoms therefore, leads to delays in appropriate diagnosis and

treatment, a situation, Insel argues, that is akin to waiting for a myocardial infarction before treating the underlying cause. This position has important implications for early detection and early intervention. However, it also leads to the perception that the emotions and their disorders are divorced from physical health, a perception that could not be farther from the truth, as we will demonstrate here. An excellent candidate for providing a critical structural link between psychological moments and mortality is heart rate variability (HRV), a proposal we label as Neurovisceral Integration Across a Continuum of Time (or NIACT) and describe in the present manuscript. HRV refers to the millisecond variation between consecutive heartbeats and reflects the pulse of vagal nerve activity on the sinoatrial node. The word "vagus" is Latin for wandering, referring to the extensive distribution of the vagus nerve (cranial nerve X) throughout the body.

Research on HRV has focused on a wide range of behaviours including positive mood states (Kok & Fredrickson, 2010; Kok et al., 2013; Oveis et al., 2009), emotion regulation (Butler, Wilhelm, & Gross, 2006; Di Simplicio et al., 2012; Geisler, Vennewald, Kubiak, & Weber, 2010), cognitive function (Hansen, Johnsen, & Thayer, 2003; Hansen, Thayer, Johnsen, Sollers, & Stenvik, 2004; Suess, Porges, & PLUDE, 1994), as well as a variety of biological functions including metabolic homeostasis (Tracey & Pavlov, 2012), inflammatory processes (Tracey, 2002) and even brain plasticity (Hays, Rennaker, & Kilgard, 2013). Alterations in HRV may also underpin a host of conditions and diseases including psychiatric illness and cardiovascular disease (Kemp & Quintana, 2013; Thayer, Yamamoto, & Brosschot, 2010c), while stimulation of the vagal nerve has been used as a treatment for refractory epilepsy (Shahwan, Bailey, Maxiner, & Harvey, 2009) and depression (Rush et al., 2005), and may even be beneficial for other conditions including tinnitus, chronic hiccups and Alzheimer's disease (see Clancy, Deuchars, & Deuchars, 2013 for review). It is surprising therefore that the implications of vagal involvement in such a wide variety of functions, behaviours and conditions are seldom extrapolated beyond the specific field in which the individual studies have been conducted. To that end, we bring together the many strands of research conducted across a variety of research fields, and provide an interpretative framework through which these findings may be understood. This extended neurovisceral integration model (or NIACT), emphasises the importance of neurovisceral integration over time, such that the extent to which the brain and body are integrated will contribute to eventual mortality.

The overarching aim for this review is to provide a multidisciplinary synthesis and framework through which the extensive, yet disparate, body of evidence on the role of HRV in a variety of psychological functions, inflammation, illness and disease may be understood. In the sections that

follow we first describe the theoretical background on which many prior studies have been interpreted. Major theoretical models include the neurovisceral integration model (Thayer & Lane, 2000; 2009) and the polyvagal theory (or PVT) (Porges, 1995; 2011), which characterise the neural circuitry underpinning behavioural flexibility to environmental change and social engagement. While these models have important implications for mental and physical health, a comprehensive model based on the most recently published evidence, linking psychological moments to morbidity and mortality remains to be proposed. This is the major rationale for writing the present paper. Following this discussion, we provide an interpretative framework that emphasises the link between vagal function and HRV, highlighting that all measures of HRV typically index parasympathetic nervous system (PNS) function, albeit distinct physiological mechanisms. This section also provides an important background for readers who may be unfamiliar with the intricacies of HRV research, and the ways in which data has been collected and interpreted (see also Table 1). Our model conceptualises HRV as a psychophysiological marker of health and wellbeing, and this conceptualisation has wide applicability. We therefore devote the next section of our paper to the evidence supporting this claim, highlighting that physical activity, improving diet quality, consuming alcohol in moderation and reducing tobacco consumption are all associated with increased vagal function. However, health behaviour is not the only factor influencing vagal function, leading us to our next section, which focuses on psychological moments including the broad constructs of emotion and cognition. We suggest that vagal function may provide the physiological foundation on which psychological functioning is supported, while stable changes in resting-state vagal function will have direct implications for future health. The following section describes some overlapping processes that may link these moment-to-moment (phasic) changes that support psychological functioning to stable changes in resting-state vagal function. Several conceptually related processes including self-perpetuating feedback loops and allostatic regulation underpinning experience-dependent change are described. A critical regulatory role for the vagus nerve over a variety of tightly integrated allostatic systems is described highlighting an important role for what has been described as the cholinergic anti-inflammatory reflex. Vagal dysfunction – indexed by reduced resting-state HRV – will lead to allostatic load, increasing morbidity and mortality, the focus of the following section. The association between vagal function and psychiatric disorders and their treatments is described, followed by a discussion on the intimate relationship between psychological and physical health and wellbeing, highlighting links between vagal function and future health. We then synthesize the body of literature reviewed in preceding sections and present our model we label as Neurovisceral Integration Across a Continuum of Time (or NIACT). This model emphasizes vagal function as a critical, missing link in prior accounts that

have sought to link and bridge the gap between psychological functioning and mortality. A variety of theoretical conundrums and methodological limitations are then described providing a foundation on which future research could be based.

Our paper makes an important contribution to the existing literature on HRV by emphasizing the role of a temporal continuum that spans psychological moments through to mortality. Several points regarding our review should be noted. First, we describe and discuss studies from diverse fields including health psychology, emotion and cognitive science, neuropsychiatry, epidemiology and public health. Accordingly, a comprehensive review of the literature in regards to vagal function is beyond the capacity of the current paper. Instead, we draw upon recently published reviews within each domain and research field, and highlight findings from more recent studies that build upon these reviews. Second, we make an important distinction between phasic and tonic HRV, emphasizing a principle of demand appropriate responsiveness, in order to better interpret and appreciate the significance of increases or decreases in HRV within and between particular groups and conditions. Pragmatic and theoretical distinctions are made between HRV collected under different recording conditions (i.e. resting state, task and recovery conditions). In this regard we propose that resting-state HRV may reflect the combined impact of multiple psychological moments, providing the best indication of future health. By contrast, we suggest that task-driven activity reflects autonomic responsiveness to that with which the individual is engaged, while recovery-related activity may reflect emotional resilience (mental toughness), particularly after a stressor. Throughout this paper we emphasize reported effect sizes rather than statistical significance where possible, consistent with increasing calls for meta-analytic thinking (Cumming, 2014; Lakens, 2013). Effect sizes are interpreted in the context of other similar studies and the way in which the authors of specific papers have interpreted their own findings.[1]

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

Theoretical Background

[1] When necessary, we drew upon the benchmarks provided by Cohen (Cohen, 1988), which can be grouped into two families, the *d* family, which relate to standardized mean differences (small, $d = 0.2$; medium, $d = 0.5$; large, $d = 0.8$), and the *r* family, which is related to strength of association (small, $r = 0.1$; medium, $r = 0.3$; large, $r = 0.5$).

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

The NIM (Thayer & Lane, 2000; 2009) describes an inhibitory, cortico-subcortical neural circuit that integrates brain and body function, and supports a variety of functions including emotion, cognition, and social behaviour. Some of the studies supporting links between vagal function and these psychological moments are described in following sections. The central autonomic network (or CAN) (Thayer & Lane, 2000; 2009) is responsible for the inhibition of medullary cardioacceleratory circuits, for controlling psychophysiological resources and appropriate responses to environmental change. HRV indexes vagal inhibition of the heart and reflects the primary output of the CAN. Neuroimaging studies (B. Allen, Jennings, Gianaros, Thayer, & Manuck, 2014; C. Chang et al., 2013a; Thayer, Ahs, Fredrikson, Sollers Iii, & Wager, 2012) have begun to explore the association between neural correlates of resting state HRV (B. Allen et al., 2014; C. Chang et al., 2013a) as well as HRV reactivity (Thayer et al., 2012) (see also Beissner, Meissner, Bär, & Napadow, 2013). These studies have demonstrated that higher resting-state HRV is associated with greater resting cerebral blood flow (B. Allen et al., 2014), a finding that may reflect a coordinated physiological substrate for diminishing sympathetic adrenergic inhibition in the nucleus ambiguous and reducing sympathetic vasoconstriction of cerebral arteries during the resting state. By contrast, meta-analysis of HRV reactivity during cognitive, sensory/motor and emotion processing (i.e. task-evoked changes in HRV) reveal a number of regions within the cortical-subcortical pathway including the ventro-medial prefrontal cortex and amygdala (Thayer et al., 2012). According to this model, the CAN shapes brain activity and associated autonomic responses in the body. Therefore, vagal impairment is associated with prefrontal hypoactivity, amygdala hyperactivity and low resting-state HRV contributing to a predisposition to threat perception and inflated negativity biases. By contrast, healthy vagal function will be associated with flexible prefrontal inhibitory control over amygdala function and flexible adaptation to environmental change. Interestingly, resting-state studies (e.g. B. Allen et al., 2014) have also demonstrated that higher resting HRV is associated with lower cerebral blood flow in regions previously implicated in cardiac vagal reactivity (Thayer et al., 2012). More specifically, higher resting HRV is associated with less relative perfusion in left amygdala, left putamen, right hippocampus, left parahippocampal gyrus, left and right insula, and two subregions of the right superior temporal gyrus (B. Allen et al., 2014). Thus, lower resting cerebral blood flow in these areas could be maintaining high levels of resting

HRV, while disinhibition of these areas and associated cardioacceleratory circuitry would lead to decreased HRV under challenge. The NIM emphasizes the intimate relationship between brain and body, and suggests that HRV may index 'top-down' appraisals, which is mediated by the capacity with which the ventro-medial prefrontal cortex is able to inhibit subcortical pathways.

The second theory – PVT – is complementary to the NIM, emphasising a phylogenetic shift in the control of the autonomic nervous system (ANS) from the dorsal motor nucleus of the vagus in reptiles to the nucleus ambiguous in mammals (Porges, 1995; 2011). According to the PVT, one consequence of the transition is the emergence of social behaviour including facial expression and vocalisations. The vagus nerve is either myelinated or unmylinated (i.e. polyvagal), and the model characterises a role for the unmyelinated vagus in phylogenetically older immobilisation behaviours (e.g. extreme terror, neurogenic bradycardia, vasovagal syncope, reproduction, nursing and pair-bonding), while the myelinated vagus is linked to evolutionary younger behaviours (e.g. emotion, social communication and psychophysiological flexibility). It is the myelinated vagus nerve that is linked to HRV and although this aspect of the theory has been challenged (e.g. Berntson, Cacioppo, & Grossman, 2007; Grossman & Taylor, 2007), the psychological and behavioural implications of the theory have been labelled "as something of a sacrament." (Berntson et al., 2007). The model describes a trinity of nuclei in the medulla including the dorsal motor nucleus of the vagus (DMNX), the nucleus ambiguous (NA) and the nucleus tractus solitarius (NTS). The unmyelinated vegetative vagus nerve originates from the DMNX, while the myelinated 'smart' vagus originates from the NA from which vagal efferent pathways project. The final structure in the trinity is the NTS, which is the primary site for termination and integration of many afferent pathways traveling from peripheral organs, allowing for subsequent regulation of behaviour.

These theories have helped to contextualise many of the published findings in the literature. Both are complementary, and in fact, draw upon Hughlings Jackson' principle of hierarchical integration through inhibition (J. H. Jackson, 1958) in which removal of inhibition 'permits' rather than 'elicits' increased physiological activity (i.e. disinhibition) (Porges, 2011; Thayer et al., 2012). A typical defensive response is associated with a reciprocal pattern of vagal inhibition and sympathetic excitation, accompanied by increased heart rate and blood flow, and inhibition of the baroreflex, which increases blood pressure (Berntson, Cacioppo, & Quigley, 1991). The autonomic nervous system (ANS) may also be co-activated or co-deactivated (Berntson et al., 1991; Berntson, Cacioppo, & Quigley, 1993). Co-activation of the parasympathetic and sympathetic nervous systems (PNS and SNS) may help mitigate the deleterious effects of increased SNS activity

(Norman et al., 2011), while sympathetic-parasympathetic cardiac deactivation may reflect passive sensory intake (Kreibig, 2010). Recent thinking further indicates that vagal activity may actually be withdrawn without activation of the SNS (Porges, 2011). This metabolically conservative response to challenge (vagal withdrawal without subsequent SNS activation) may also reflect the mood and anxiety disorders during resting state (Kemp, Brunoni, et al., 2014a). Both models emphasise different aspects of adaptation and engagement. NIM highlights the importance of the prefrontal inhibition over lower subcortical pathways in shaping brain activity and subsequent autonomic responses, while PVT emphasises the emergent properties of phylogenetically older neural circuits (i.e. "flight", "fight" or "freeze") when phylogenetically younger circuits critical to social engagement fail to function. According to NIM, higher levels of resting-state HRV reflect stronger 'top-down' appraisal and prefrontal inhibition of cardioacceleratory circuitry. By contrast, the PVT links higher levels of HRV to capacity for social engagement and phylogenetically younger behaviours.

Summary

Major characteristics, core components and associated behaviours highlighted in these models are summarised in Figure 1. Prosocial behaviour is associated with cortical inhibition of the central nucleus of the amygdala (CeA), activation of the vagus nerve within the nucleus ambiguus—increasing vagal tone—facilitate socially engaging facial expressions, leading to positive social interactions. The NST receives vagal afferent feedback from the viscera and internal milieu, and this information is then directed to cortical structures responsible for the top-down, flexible regulation of emotion (Fig 1, black arrows). Increased activation of the vagus nerve therefore facilitates social engagement and positive emotion (discussed further below). By contrast, responsiveness to environmental challenge (e.g. orienting) and withdrawal from the environment (e.g. fear) will be associated with a disinhibition of CeA (the major efferent source for modulation of cardiovascular, autonomic and endocrine responses) and vagal withdrawal—decreasing vagal tone—triggering fight-flight-or-freeze responses. Again, information relating to the status of the viscera and internal milieu are fed back to the nucleus of solitary tract and the cortex, allowing for subsequent regulation of the emotion response (Fig 1, grey arrows). Decreased activation of the vagus nerve therefore facilitates fight-flight-or-freeze responses and negative emotions. Although both theories have important implications for mental and physical health, a comprehensive model linking these everyday psychological moments and phasic vagal alterations to morbidity and mortality remains to be described; this is the task of the current paper. An interpretative framework

for HRV measures will now be described after which, relevant studies on HRV from diverse fields of scientific endeavour will be discussed.

INSERT FIGURE 1 ABOUT HERE

HRV and Vagal Function: An Interpretative Framework

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

The standard deviation of N-N intervals (SDNN) is a commonly reported, time-domain measure, reflecting all cyclic components responsible for variability. SDNN extracted from long-term recordings (usually 24-hours) is a robust predictor of adverse cardiovascular events and mortality (Hillebrand et al., 2013; Huikuri & Stein, 2013). Commonly reported measures of HRV from short-term recordings (2 – 15mins) include the root mean square of successive differences (RMSSD) and high frequency HRV (HF-HRV). While RMSSD – a time-domain measure – and HF-HRV are highly correlated, the former is less affected by changes in breathing frequency (Penttilä et al., 2001; Saboul, Pialoux, & Hautier, 2013), highlighting the utility of this measure during ambulatory studies, and in patient populations such as those with an anxiety disorder. Another commonly reported measure of vagal function is respiratory sinus arrhythmia (RSA), a measure that combines heart rate with respiration data, and like HF-HRV reflects the ebb and flow of heart rate associated with respiration. There has also been much research interest in non-linear measures of HRV, which assess qualitative properties rather than the magnitude of heart rate dynamics, and may better distinguish between groups, however their physiological basis is less clear. For more information on collection, extraction and interpretation of these measures, interested readers are referred to past

reviews on this topic (Appelhans & Luecken, 2006; Berntson et al., 1997; Rajendra Acharya, Paul Joseph, Kannathal, Lim, & Suri, 2006; Reyes Del Paso et al., 2013; Shaffer, McCraty, & Zerr, 2014; Thayer, Hansen, & Johnsen, 2010a; Thayer, Hansen, Saus-Rose, & Johnsen, 2009).

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

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

Summary

In summary, commonly reported measures of HRV include SDNN, an estimate of all cyclic components responsible for variability often reported in studies that have collected data from longer-term recordings (usually 24-hours), and RMSSD and HF-HRV, measures of fast changes

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

Vagal Function and Health Behaviour

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

basis through which the effectiveness of other behavioural interventions (e.g. massage, exercise, meditation, yoga and HRV biofeedback) may be understood.

In a study conducted more than 25 years ago (Hayano et al., 1990), it was concluded that smoking causes an acute and transient decrease in vagal function as measured by RSA, while heavy smoking causes long-term reductions (RSA) as well as blunted postural responses in autonomic cardiac regulation (i.e. postural changes were not observed in heavy smokers as defined by >25 cigarettes per day). Strikingly, more recent research has even reported that non-smokers exposed to environmental tobacco smoke at home or work for more than 2 hours a day (n=80) – relative to the unexposed (n=1034) – display a 2.7% higher heart rate (Felber Dietrich et al., 2007), in addition to a 15% reduction in total power, LF-HRV, low/high frequency ratio and ultralow frequency power of HRV. These findings were not simply acute responses as findings associated with the sleep period were similar to the results from the 24-h measures. Depressed smokers even display decreases in a variety of HRV measures – extracted from recordings during a 5-minute resting period – in depressed patients (N=77) (Harte, Liverant, Sloan, & Kamholz, 2013). These findings are particularly striking considering that depressed patients are already characterised by low HRV (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012a; Kemp et al., 2010; Kemp, Quintana, Quinn, Hopkinson, & Harris, 2014d) (discussed further below). Depressed smokers (n=34) display decreased HF-HRV (η^2_p = 0.11) and RSA (η^2_p = 0.13), relative to depressed non-smokers (n=43), even after controlling for demographic and medical characteristics, and medication use (Harte et al., 2013). Another recent study by the same authors (N=62) (Harte & Meston, 2014) demonstrated that successful quitting (n=20) was associated with increases in HRV at follow-up, 4-weeks after patch discontinuation. Results from this study were based on RMSSD and HF-HRV extracted from a 3-minute baseline period involving presentation of a documentary film (Cohen's *d*'s ranged from 0.50 to 0.73). By contrast, HRV indices among unsuccessful quitters were generally unchanged across time.

Physical activity is associated with a decreased heart rate and increased HRV during the resting state, effects that likely contribute to improvements in mental and physical health over the longer term (see Carter, Banister, & Blaber, 2003; Thayer, Yamamoto, & Brosschot, 2010c). Thayer and colleagues were among the first to report that fit individuals (n=18) – from a group of university students aged 17 to 25 years – display greater vagal control of the heart relative to low fit individuals (n=16), as determined by time and frequency domain measures of HRV, even after controlling for body mass index (BMI) (Rossy & Thayer, 1998). Fitness was determined using a

questionnaire that estimates VO_{2max} based on subjective report of physical activity, age, body composition and sex, while HRV was calculated during a resting baseline period, a face-cooling task designed to elicit parasympathetic activity, a reaction time task designed to elicit primarily sympathetic activity, a combination task that was designed to elicit a combination of both parasympathetic and sympathetic activation, and recovery periods after each task. The key finding – increased vagal function in high fit individuals relative to low fit individuals – was observed at baseline and across all tasks, demonstrating the robustness of these findings (Cohen's *d* for HF = 0.61 relating to the main effect of fitness).

A study on the Whitehall II cohort (N=3,328) of older civil servants aged 45-68 years (Rennie et al., 2003), showed that moderate and vigorous activity is associated with higher HRV and lower heart rate during a 5-minute resting-state, and these findings remained significant after adjustment for smoking and alcohol intake. Men whose BMI was greater than 25kg/m^2 and engaged in vigorous activity displayed similar HRV levels to normal-weight men who did not engage in vigorous activity. Activity levels in this study were determined by a questionnaire that allows for a metabolic equivalent (MET) value to be determined, such that 1 MET corresponds to the metabolic energy expended lying quietly (equivalent to 1 kcal per kilogram of body weight per hour). Vigorous activity was defined as greater than or equal to 5 MET hours per week (Rennie et al., 2003). A randomized-controlled study on sedentary young adults (N=149, mean age 30 yrs) reported that 12-weeks of aerobic conditioning, but not strength training enhances autonomic control of the heart, as determined by decreases in heart rate (3.49 beats per minute or BPM) and increases in HF-HRV (0.25 natural log (ln) msec^2) during 10-minutes of quiet rest (R. P. Sloan et al., 2009). These authors further reported that 4-weeks of deconditioning following the training period led to these autonomic measures returning to pre-training levels.

Research also demonstrates that regular exercisers (n=22) – participants engaging in at least 30 mins of vigorous activity, three times per week – display a more resilient cardiac stress response than irregular exercisers (n=18) (*d* = 0.48) (Hanson, Outhred, Brunoni, Malhi, & Kemp, 2013). Participants in this study were required to complete a serial-13's subtraction task, a task adapted from the Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993). Regular exercisers displayed a resting heart rate of 66 BPM, while irregular exercisers displayed a resting heart rate of 72 BPM (*d* = 0.55). Interestingly, regular vigorous exercisers also reported feeling less stressed during this task. Furthermore, escitalopram, a commonly prescribed selective serotonin reuptake inhibitor (SSRI), attenuated the cardiac stress response (heart rate decreased, *d* = 0.80, while HRV

increased, d = 0.33) associated with a mental arithmetic task in irregular exercisers to the same level as that displayed by regular exercisers under placebo. These salubrious effects of exercise may even extend to the intrauterine environment. A study (N=61) examining the effects of aerobic exercise during pregnancy (>30 min of aerobic exercise, 3 X per week) reported beneficial effects on fetal cardiac autonomic control of heart rate and its variability (May, Glaros, Yeh, Clapp, & Gustafson, 2010). This study utilised a dedicated fetal biomagnetometer to record magnetocardiograms to detect and separate the fetal cardiac signal from the maternal signal. Fetal heart rate was lower (d = 1.54) and HRV higher (HF-HRV, d = 0.95) in the exercise group as compared to foetuses of non-exercising women during an active fetal state. In a follow-up study by the same authors, infants born to women who exercised during pregnancy display higher RMSSD, LF and HF power (May, Scholtz, Suminski, & Gustafson, 2014) indicating that the developing cardiac ANS is sensitive to effects of maternal physical activity beyond the womb.

At the other end of the lifespan, greater leisure-time activity, walking distance and walking pace are associated with more favourable HRV indices in older adults (N=985) after multivariable adjustment (Soares-Miranda et al., 2014). It is worth noting here that this study was conducted in adults aged more than 65 years, and caution is advised when interpreting HRV measures collected from the elderly as higher levels of HRV may actually reflect abnormal sinus patterns, especially when the underlying organisation has not been examined using power spectral methods or other graphic methods (Huikuri & Stein, 2013). So in the study with older adults (Soares-Miranda et al., 2014), while higher 24-hour SDNN and ultra-low frequency power were prospectively associated with greater total leisure-time, walking distance and walking pace, lower normalized HF-HRV was also observed in those that increased walking pace between baseline (1989-1990) and at the follow-up period (1992-1993). While this was an unexpected finding, the authors argued that this finding might also reflect less erratic HRV in their older cohort. It is noted however, that the authors only excluded participants with markedly irregular cardiac rhythms indicated by "extent of irregularity of the rhythm or p waves that was [*sic*] too high for trained personnel to accurately label which beats were normal sinus beats." It is possible that the focus on the elderly in addition to inclusion of those individuals with less marked, yet irregular, cardiac rhythms could have contributed to these findings. These findings further highlight the utility of short, standardised recordings over 24-hour recordings which provide more standardised recordings of resting-state activity.

Vagal function is also improved by dietary changes, including consumption of fruits and vegetables, moderate alcohol consumption and intake of omega-3 fatty acids and vitamin D through fish and

nut consumption (see Thayer, Yamamoto, & Brosschot, 2010c for review). Atlantic salmon served three times per week from September to February is associated with significant improvements in RMSSD (d = 0.69) and heart rate (d = 0.45), as well as decreases in state-anxiety (d = 0.45) in forensic inpatients (N=95) (Hansen et al., 2014). This study also reported a positive relationship between RMSSD and vitamin D status (r = 0.27). A recent meta-analysis (Xin, Wei, & Li, 2013) on 15 randomised controlled trials (N=692) reported that short-term term effects of fish-oil supplementation (6-24 weeks) increased HF-HRV (d=0.30), while effects on other measures including SDNN and RMSSD were not significant. The authors suggested that this observed increase in HRV may underpin the antiarrhythmic and other clinical effects of fish oil. Other research (Soares-Miranda et al., 2012) has demonstrated that trans-fatty acid consumption – and higher plasma phospholipid and erythrocyte membrane 18:2 TFA (*trans*-18:2) consumption in particular – is associated with specific, less favourable indices of HRV in young (N=160) and older (N=461) adults. It is relevant to note here that *trans*-18:2 is also associated with increased risk of coronary heart disease and sudden cardiac arrest (e.g. Lemaitre et al., 2006).

Finally, there is increasing evidence for the beneficial effects of a variety of complementary and alternative medical therapies (e.g. meditation, acupuncture) on vagal function (see Oke & Tracey, 2009 for review). A course of integrative mind-body training (IBMT), a technique adapted from traditional Chinese medicine that incorporates meditation and mindfulness practices, leads to a host of physiological changes (N=43; n=20 in the IBMT group) including improved vagal function during and after 5-days of training in this technique. As little as 20 minutes of practice per day lowered heart rate (d = 1.65) and sweat response, increases HRV (d = 1.44), and results in deeper and calmer breathing relative to a relaxation control group (Tang et al., 2009). Another study on the impact of intensive 10-day Vipassana meditation (N=36) reported similar increases in the normalised, HF-HRV (d = 0.57) during meditation following the retreat, consistent with prior studies including that of Tang and colleagues (Tang et al., 2009; Wu & Lo, 2008). Decreases in the LF-HRV were also observed (d = 0.73), a finding that has been linked to vagally-mediated, baroreflex outflow (Reyes Del Paso et al., 2013). These findings were interpreted in the context of positive and full immersion in an activity, a psychological phenomenon labelled as ‘flow’ (Csikszentmihalyi, 2002).

Summary

These studies highlight the beneficial effects of a variety of health behaviours on vagal function, reinforcing the conceptualisation of HRV as a psychophysiological marker of health and wellbeing.

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

Vagal Function and Psychological Moments

Vagal Function, Emotion and its Regulation

Although research on emotion has increased exponentially over the last decade, the term ‘emotion’ remains ill-defined, and this situation has led to an “intellectual stalemate” (LeDoux, 2012) leading some to liken the situation to the Hundred Years’ War between England and France (Lindquist, Siegel, Quigley, & Barrett, 2013). We suggest here that this stalemate may, in part, relate to modern neuroscientific research focusing on the brain, while the contributions from the body have been largely sidelined. Bidirectional communication between the brain and body play an important role in emotion and its regulation, such that the brain impacts on the body via visceral efferent pathways, and the body impacts on the brain through afferent feedback (Kemp, Krygier, &

Harmon-Jones, 2014b). It is possible therefore that the extent to which emotion is able to be effectively regulated will depend on the extent of central-peripheral neural feedback and CAN-ANS integration, as indexed by HRV (Thayer & Friedman, 2002; Thayer & Lane, 2009). However, emotion is typically interpreted through the lens of the SNS (Porges, 2011), as first described by Cannon (Cannon, 1927) and subsequently by Selye (Selye, 1936; 1956). Consistent with this approach, modern research has generally focused on cortical arousal using a variety of neuroimaging techniques to assess brain function, with little attention to the distinction between excitation and inhibition (Porges, 2011). However, the theoretical frameworks – NIM and PVT – described above, emphasise an important inhibitory role over cardioacceleratory structures allowing for the regulation of subsequent behaviour.

An important component of emotion and social cognition is the capacity to determine what the other is thinking by recognizing and interpreting subtle facial cues, which subsequently guide emotional and behavioural responses to others in the environment. An association between HF-HRV extracted from 5-minute resting-state recordings and performance on a subsequent emotion recognition task (r = 0.26) has been reported (N=65) (Quintana, Guastella, Outhred, Hickie, & Kemp, 2012). This study highlighted for the first time, a role for vagal function in the ability to recognise emotion expressions from the eye region. Consistent with PVT (Porges, 2011), these findings indicate that emotion perception is facilitated by a calm physiological state and effective inhibition of the SNS. This possibility is supported by an earlier study (Bal et al., 2009) on children with autism spectrum disorders (ASD) (n=33), a condition characterised by impairments in social functioning. This earlier study reported that children with ASD display decreased resting HRV (as measured by RSA during the resting state) (d=0.48) and increased heart rate (d=0.55), relative to a control group of typically developing children (n=45), reflecting a generalised, psychophysiological state that may inhibit capacity for social interaction. HRV in this study (Bal et al., 2009) was extracted from a 2-minute baseline period in which participants were in a generally stable and calm state. Consistent with our later study in undergraduate students (Quintana et al., 2012), the authors also observed that higher RSA was associated with faster emotion recognition.

An increasing body of research has highlighted a relationship between resting-state HRV and measures of positive mood (Geisler et al., 2010; Geisler, Kubiak, Siewert, & Weber, 2013; Oveis et al., 2009; Z. Wang, Lü, & Qin, 2013) (but see Silvia, Jackson, & Sopko, 2014). A study on 80 young adults (Oveis et al., 2009) reported that RSA – measured during a 90-sec resting state (RSA_{REST}) – is related to self-reported extraversion (r = 0.37), agreeableness (r = 0.22), optimism (r

= 0.27), state positive affect (r = 0.36) and lower neuroticism (r = -0.21). Importantly, RSA_{REST} was not associated with increased positive emotion, or stimulus-specific emotion, in response to compassion-, awe-, or pride-inducing stimuli. Nor was RSA_{REST} associated with negative mood. A study on 172 university student participants demonstrated that HF-HRV – measured during a 7-min resting state – was associated with subjective wellbeing (r = 0.16, 0.17) (Geisler et al., 2010). This study further reported that the relationship between HRV and wellbeing was mediated by emotion regulation strategies, an observation we discuss further below. A more recent study by the same authors (Geisler et al., 2013) on 125 undergraduate students reported that HF-HRV – again, measured during a 7-min resting state – is correlated with self-reported social behaviours including engagement (r = 0.33), social-support seeking (r = 0.23), social integration (r = 0.29) and social acceptance (r = 0.25). Another study (Z. Wang et al., 2013) on 98 young adults reported that HF-HRV – measured during a 5-min baseline period – was correlated with positive (r =0.31), but not negative (r = -0.03) affectivity. A recent study (Silvia et al., 2014) however, reported that HF-HRV, RMSSD and other time-domain measures of HRV measured during a 6-minute 'vanilla' baseline do not predict any measures of positive mood states including personality traits and a variety of self-reported, positive emotions (N=239). (Effect sizes of observed correlations ranged from zero to small.) These null findings highlight the limitations of between-subject designs, which are characterised by less optimal experimental control.

Several published studies benefiting from repeated assessment of the same individuals are worth noting here. The first study (N=65) (Kok et al., 2013) involving random allocation of participants to a course in loving-kindness meditation (LVK) or control reported an increase in positive emotions in those allocated to LVK, an effect that was moderated by baseline vagal activity. Two-minute recordings were collected during the resting state to extract HF-HRV and RSA before the LVK workshop. This study further observed that increased positive emotions led to additional increases in vagal activity (resting-state HRV was collected a second time following the LVK intervention), a finding mediated by increased perceptions of social connections. Extending on findings reported in their earlier study (Kok & Fredrickson, 2010), these authors built a parallel-process mediation model to test the hypothesised bidirectional causal chain between emotion and vagal function. Importantly they ruled out five additional alternative models that could have potentially explained their findings. The authors conclude that positive emotions build physical health, and that the bidirectional relationship between emotion and vagal function supports a conceptual model involving a self-sustaining, upward-spiral dynamic. It is possible that this bidirectional relationship also applies to negative emotions in which negative emotion and vagal function may lead to a self-

sustaining, downward-spiral dynamic perhaps contributing to impaired emotional regulation capacities characteristic of many psychiatric disorders. Another study on 60 healthy adults demonstrated that deactivated positive affect (i.e. relaxed, content, even-tempered, calm), but not activated positive affect (i.e. dynamic, active, awake, brisk, delighted) is associated with higher nocturnal vagal tone (HRV: r = 0.28; heart rate: r = -0.36) (Schwerdtfeger, Friedrich-Mai, & Gerteis, 2014). In this study, measures were extracted from ECG data collected between 1 to 5am. Surprisingly, no association between negative affect and cardiac variables were obtained in that study (Schwerdtfeger et al., 2014). The authors interpreted their findings along a causal pathway from positive emotion to health, in the context of other evidence (Ben-Dov et al., 2007) that reported elevations in nocturnal heart rate and attenuation in its variability increase risk for all-cause mortality.

Interestingly, while *positive mood* appears to be associated with increased vagal function, *positive emotions* are associated with vagal withdrawal, highlighting the principle of context appropriate responsiveness. Research has demonstrated that recall and experiential reliving of happiness is associated with an increase in heart rate and decrease in its variability (Rainville, Bechara, Naqvi, & Damasio, 2006). This study (N=43) also reported an increase in heart rate for all emotions (anger, fear, happiness and sadness); only fear and happiness displayed decreases in HF-HRV. In another study, the cardiorespiratory effects of musically induced emotions were related to the "arousal" dimension, rather than the "valence" dimension of emotion (Nyklíček, Thayer, & Van Doornen, 1997), providing one explanation in which to understand the effects of positive emotions – rather than mood – on vagal function. A more recent study on 83 healthy, young-to-middle aged participants (Overbeek, van Boxtel, & Westerink, 2012) reported strong overall heart rate deceleration from baseline level to presentation of pictures as well as film fragments (η^2_p = 0.626), while HRV measures (and frequency domain measures in particular) displayed a decrease (η^2_p ranged from 0.077 to 0.229) during exposure to film fragments – but not to pictures – regardless of the specific emotion. These heart rate decelerations reflect an 'orienting' response that facilitates information processing of external stimuli (note that heart rate was increased during recall and experiential reliving of emotion, (Rainville et al., 2006)), while changes in HRV measures were observed to relate to increased respiration rate during presentation of films (η^2_p = 0.457). Heart rate and HRV are also particularly sensitive to anxiety and stress (see Fig 2); for example, strong increases in heart rate (d = 4.476) and decreases in HRV (d = 2.895) are observed during completion of a serial-thirteens subtraction task (Hanson et al., 2013; Kemp, Outhred, et al., 2014c), a commonly used stressor (Kirschbaum et al., 1993). These findings highlight the importance of

distinguishing between an emotion, especially positive emotions, and mood, a relatively longer-lasting and more diffuse emotional state.

INSERT FIGURE 2 ABOUT HERE

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

Resting heart rate and HRV however, do not simply reflect emotional state per se. In fact, a body of research indicates that resting-state measures contribute to an individuals capacity for executive control in the face of emotional stimuli (Geisler et al., 2010; Krypotos, Jahfari, van Ast, Kindt, & Forstmann, 2011) (see also Geisler et al., 2013; Meule et al., 2013). A study on 172 university student participants demonstrated that HF-HRV – measured during a 7-min resting state – was not only associated with subjective wellbeing (r = 0.16, 0.17), but that these effects were completely mediated by executive emotion regulation strategies such as inhibition, planning and mental shifting (Geisler et al., 2010). This study concluded that their findings provide support for the proposal that resting HRV indexes self-regulatory strength, involving the ability to exert self-control and override one's dominant response tendencies. Another study on 54 young adult participants reported that response inhibition during an emotional stop-signal task was slower in individuals low on HRV (baseline RMSSD from a 10-min ECG recording) (n=27), relative to those high on HRV (n=27) (d = 0.91), in the presence of negative emotion, but not neutral stimuli (Krypotos et al., 2011). Response inhibition is a core feature of executive control and the capacity for flexible behaviour in response to a changing environment. This study suggests therefore, that individual differences in HRV may underpin differential cognitive control processes, including the inhibition of motor responses, in the presence of emotional stimuli.

Studies have also demonstrated that HRV is modulated during tasks requiring emotion regulation, such that HRV increases reflect successful engagement of cognitive inhibitory processes, while decreases may reflect impairment in these processes. When women engage in an initial negative task, HF-HRV increases during discussion of an ongoing marital disagreement (Smith et al., 2011), compared to that collected during a baseline condition, a finding that may reflect greater self-regulatory effort associated with maintaining marital quality. By contrast, women who engage in an initial neutral or positive task displayed a decrease in parasympathetic activity during the disagreement, a response that is a characteristic cardiac response to stress. Baseline HF-HRV also positively correlates with wives' self-reports of relationship depth and positivity. Similarly, baseline HF-HRV is associated with husbands' self-reports of positivity, and is also, inversely associated with self-reports of negativity. Intriguingly, a positive correlation between husbands' and wives' resting HF-HRV is also observed suggesting synchronisation between individual physiological states, an intriguing possibility that deserves further study. In another study on 33 individuals from the general population (Di Simplicio et al., 2012), individuals scoring low on the personality trait of neuroticism displayed increases in HF-HRV when down-regulating negative affect during viewing of negative pictures, relative to passive image viewing. By contrast, individuals scoring high on neuroticism displayed an opposite tendency. The authors concluded that reductions in HF-HRV during cognitive regulation of negative emotional stimuli may reflect a distinct impairment in cognitive inhibitory responses over negative affect, consistent with reduced flexibility in vagal function. Another study (Berna, Ott, & Nandrino, 2014) on 63 undergraduate students demonstrated that while HF-HRV decreases from baseline to film-elicited negative emotion (anger), it increases during recovery, but these increases were only observed in individuals categorised as having low levels of emotion regulation difficulties (ERDs). Those with high levels of ERDs displayed a persistent low HF-HRV during recovery, which may again relate to impairment in regulatory processes and low-levels of resilience to fleeting emotion. Finally, individuals with higher tonic HRV display phasic HRV enhancement during selective attention (when task-related stimuli are superimposed on fearful distractor stimuli), however, those with lower tonic HRV display phasic HRV suppression (N=77) (G. Park, Vasey, Van Bavel, & Thayer, 2014b). These findings provide direct support for a relationship between tonic and phasic HRV, such that higher tonic HRV supports greater self-regulatory effort indicated by phasic HRV enhancement, while lower tonic HRV may contribute to autonomic stress responses indicated by phasic HRV suppression.

Summary

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

Vagal Function and Cognition

Recent epidemiological research has demonstrated that low levels of cardiovascular health are associated with future cognitive impairment (Reis et al., 2013; Thacker et al., 2014). The American Heart Association has defined the concept of ideal 'cardiovascular health' (Lloyd-Jones et al., 2010) by the presence of ideal health behaviours, which for adults includes not smoking, a body mass index <25 kg/m^2, moderate physical activity for more than 150 min/wk (or vigorous activity for more than 75 min/wk), pursuit of a diet consistent with current guideline recommendations, and ideal health factors (untreated total cholesterol <200 mg/dL, untreated blood pressure <120/<80 mm Hg, and fasting blood glucose <100 mg/dL). Epidemiological studies on large samples of young (Reis et al., 2013) and older (Thacker et al., 2014) participants now suggest that efforts to improve cardiovascular health consistent with the American Heart Association strategic goals for 2020 and beyond (Lloyd-Jones et al., 2010) may have important implications for cognitive outcomes later in life, including delaying onset of dementia.

The NIM (Thayer et al., 2009) provides a neuropsychophysiological framework in which these epidemiological findings may be understood. This model describes the CAN, which highlights a tight linkage between cardiovascular and cognitive function. The functional integrity of the CAN is indexed by HRV, which reflects the inhibitory capacity of the prefrontal cortex. A study on 311 physically disabled, community-dwelling women aged 65 and older (Dae Hyun Kim et al., 2006), reported that reduced RMSSD, NN50, and HF power – extracted from 2-hours of ECG recordings

during resting state – was associated with prevalent cognitive impairment according to the Mini-Mental State Examination. These findings were reported after adjusting for relevant demographic and clinical characteristics including subclinical inflammation (serum IL-6). Strikingly, this study reported that reduced high-frequency power was associated with a 6.7-fold increase in odds for cognitive impairment. RMSSD and NN50 were associated with 3.37- and 3.29-fold increase in odds, respectively. A major limitation of this study however, was its cross-sectional design, which did not allow the authors to determine whether reduced HRV preceded the development of cognitive impairment or how HRV changes over time and subsequently affects cognitive function.

Other research however, has shown that experimental modulation of HRV impacts on prefrontal cognitive function (e.g. Albinet, Boucard, Bouquet, & Audiffren, 2010; Hansen et al., 2004), resonating with Aristotelian thinking on the functional role of the heart (C. G. Gross, 1995). In an early study (Hansen et al., 2004) on 37 males from the Royal Norwegian Navy, physical training involving 3 hours per week of aerobic exercise was associated with increased HF-HRV (d = 0.65) – measured during a 5-min resting state – faster reaction times and more true positive responses on tests of executive function as determined through a continuous performance task and working memory test. This study involved within- (i.e. repeated assessment, before and after 4-weeks of de-training or continued training) and between-subjects factors (i.e. participants were allocated into either a trained- or a detrained group based on application for further duty). This study was the first to suggest that HRV modulates prefrontal cognitive function. More recently, a randomised-controlled study on 24 elderly participants reported that a 12-week aerobic training program increased measures of time and frequency domain HRV (d's ranged from 0.27 – 0.53) – measured during a 5-min resting state – and executive function, relative to a 12-week stretching program (Albinet et al., 2010). Aerobic training involved activities such as walking, circuit-training, step and gradual running, while stretching involved enhancing flexibility, balance and body consciousness. While HRV increased from pre-training to post-training in the aerobic group, it decreased for the stretching group (d = -0.42); findings associated with a small (for time-domain measures) to moderate (for HF-HRV) effect sizes. Strikingly, executive function – measured by the Wisconsin Card Sorting Test – improved in the aerobic group, a finding associated with a moderate effect size (d = 0.47), while performance was actually worse for those in the stretching group (d = 0.27, small effect). Together these studies (Albinet et al., 2010; Hansen et al., 2004) provide important evidence for the impact of exercise on cognitive ability.

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

So what might be the mechanism underlying these surprising associations between vagal function and cognition? Research has demonstrated a suite of molecular and neurochemical alterations to be triggered by vagal nerve stimulation (VNS) including release of norepinephrine within the LC, subsequently stimulating α_1-adrenergic receptors in the dorsal raphe nucleus leading to serotonin release (Cheyuo et al., 2011; Manta, Dong, Debonnel, & Blier, 2009). Norepinephrine and serotonin – both of which stimulate neurogenesis – are projected extensively to many parts of the brain (Cheyuo et al., 2011; Follesa et al., 2007). Neurogenesis involves increased expression of brain-derived neurotrophic factor (BDNF) (Biggio et al., 2009; Follesa et al., 2007), a key molecule involved in the regulation of metabolic efficiency, eating behavior, synaptic plasticity, and learning and memory (Gomez-Pinilla, 2008). The vagus nerve also makes extensive polysynaptic projections to the thalamus, hypothalamus, the limbic system, and the cerebral cortex (Cheyuo et al., 2011; Henry, 2002) via the NTS in the brainstem. These alterations may underpin the improvements in cognitive function (and mood) that have been associated with vagal nerve stimulation (Groves & Brown, 2005; Vonck et al., 2014).

Summary

In summary, these studies have highlighted a key role for vagal function in cognitive capacity, particularly inhibitory control and executive functions including attention and working memory. In

fact, this role may underpin recent findings linking HRV to time perception (Celleni et al., 2015), an ability crucial to adaptive behaviour and social functioning. The link between vagal function and cognition also has important implications for more effective treatments of psychiatric disorders, conditions that are characterised by cognitive impairment (e.g. Quinn, Harris, & Kemp, 2012). The role of vagal function in psychiatric illness is the issue we turn to next.

Vagal Function: A Critical Link between Psychological Moments and Mortality

Our model – outlined below – highlights an important role for vagal function across a continuum of time, linking psychological moments to increases or decreases in risk for morbidity and mortality. Vagal function provides the physiological foundation on which psychological functioning is supported, while stable changes in resting-state vagal function will have direct implications for future health. Our framework distinguishes between phasic and tonic vagal function, such that phasic increases and decreases both reflect demand appropriate responsiveness to change in the environment, while chronic increases and decreases typically reflect healthy and unhealthy vagal function, respectively. It must be noted however, that context is critical to understanding potentially contradictory findings. For instance, phasic responding under acute stress may be either increased or decreased depending on whether the individual engages in self-regulation or experiences an autonomic stress response, while caution is advised over interpreting high resting-state HRV in the elderly, which may reflect abnormal chaotic cardiac activity, especially if the data are not inspected carefully. In summary, phasic HRV changes will reflect ongoing vagal changes associated with psychological moments, while chronic vagal function – indexed by standardised, resting-state recordings – will index longer-term adaptations that will be dependent on person-specific vulnerabilities, accumulative life events – especially chronic stress – and age (over which vagal function decreases markedly). So what might be the processes linking short-term phasic changes to longer-term individual differences in resting state vagal function? Several conceptually related processes including self-perpetuating feedback loops and allostatic regulation will now be briefly described below.

The experience of contextually appropriate emotions – rather than, for example, maximising the experience of positive emotions over negative ones – is considered to reflect healthy psychological

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

The concept of allostasis describes the process of achieving stability through change, involving physiological adaptation to changing environmental conditions underpinned by coordinated responses within a tightly integrated network of neural, endocrine and immune systems (Danese & McEwen, 2012; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; McEwen, 1998). Psychological stress will elicit activation in the amygdala, triggering the locus coeruleus to induce a state of alertness and focused attention, and the paraventricular nucleus of the hypothalamus, which then coordinates a neuroendocrine response to stress sustaining increased metabolic demand. Activation of the SNS will trigger bodily responses characterized as the "fight or fight response", and an immune response (inflammation) to protect the body against tissue damage should it occur. While adaptations to environmental challenge over the short-term provide an organized and coordinated response that facilitates survival over the longer-term, chronic or repeated exposure to stressors will have detrimental physiological consequences. Enduring activation of allostatic systems will lead to structural and functional abnormalities in the nervous system, elevations in inflammatory levels and chronic activation of the HPA axis that may lead to downregulation of anti-inflammatory pathways.

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

A study by Thayer and Fischer (Thayer & Fischer, 2009) reported the first evidence for this cholinergic anti-inflammatory pathway in healthy humans while controlling for SNS activity. Vagal function (indexed by 24h HRV as measured by RMSSD) was inversely related to inflammation, indexed by plasma levels of C-reactive protein (CRP) (r = -0.19; r = -0.12, partial correlation) and white blood cell counts (WBC) (r = -0.16; r = -0.13, partial correlation). Importantly, vagal function remained inversely associated with markers of inflammation (CRP, WBC) after controlling for SNS activity, which could involve either pro- or anti-inflammatory responses. Strikingly, the difference in CRP between the lowest quartile of RMSSD and the highest quartile of RMSSD was larger than previously reported differences between current smokers and non-smokers. A more recent study by Thayer and colleagues demonstrates that HRV actually predicts CRP levels four years into the

future (r = -0.34; r = -0.20, partial correlation), thus providing the first prospective data showing that low HRV predicts increased chronic inflammation over a period of years in healthy working individuals (Jarczok, Koenig, Mauss, Fischer, & Thayer, 2014).

Summary

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

Vagal Function, Morbidity & Mortality

Vagal Function, Psychiatric Disorders & their Treatments

The association between psychiatric disorders and HRV has attracted much research attention over several decades. PVT (Porges, 2011) has linked vagal nerve outflow to social engagement, impairment in which is a major characteristic of psychiatric disorders. Related features including flattened affect, poor eye gaze, attenuated facial expressions, lack of prosody, and hyperacusis may also be underpinned by vagal impairment (Porges, 2011). The question that researchers have sought to answer, therefore, has been whether psychiatric disorders are characterized by reductions in HRV and more recently, whether HRV alterations are present during remission. While these questions have been addressed, reported findings have been contradictory. Researchers have also debated whether HRV is reduced in psychiatric disorders or whether these reductions are driven by medications for these conditions. We have sought to address these issues in a number of studies by employing meta-analytic and other techniques, allowing us to draw conclusions from the contradictory body of literature. This research on major depressive disorder (MDD) (Kemp et al.,

2010), anxiety disorders (Chalmers, Quintana, Abbott, & Kemp, 2014), schizophrenia (Clamor, Lincoln, Thayer, & Koenig, 2016), borderline personality disorder (Koenig, Kemp, Feeling, Thayer, & Kaess, 2016) and antidepressants (Kemp, Brunoni, et al., 2014a; Kemp et al., n.d.) is briefly reviewed below. All these studies have demonstrated that these disorders are associated with low HRV. In fact, an independent meta-analysis by colleagues (Alvares, Quintana, Hickie, & Guastella, 2016) has reported that HRV is reduced in all patient groups including mood, anxiety, psychosis and dependent disorders (Hedges g = -0.583) and that findings remained highly significant for medication-free patients compared to controls across all disorders. An exception to this take home message is the recent systematic review published on bulimia nervosa (Peschel et al., 2016), which reported increased – not decreased – HRV in this condition. This finding is discussed further below in the section on theoretical conundrums & methodological limitations.

The meta-analysis on patients with MDD (Kemp et al., 2010) was conducted to determine whether otherwise healthy, and unmedicated depressed patients display reductions across a variety of time-, frequency- and non-linear domain measures of HRV. This was important because cardiovascular disease may have led to overestimation of the association between depression and resting-state HRV in prior studies. An earlier study (Licht et al., 2008) based on the large Netherlands Study of Depression and Anxiety (NESDA) cohort (N= 2,373) had also recently concluded that lowered HRV in depression was mainly driven by the effects of antidepressant medications. By contrast, our meta-analysis revealed that MDD patients (n=673) did display lower HRV, relative to healthy controls (n=407), effect sizes ranging from small (based on time- and frequency-domain HRV measures; Hedges' g = -0.3 and -0.29, respectively) to large (non-linear measures; Hedges' g = -1.955, highlighting the utility of non-linear HRV measures). Depression severity was also negatively correlated with HRV ($r = -0.35$, $p < 0.001$). Tricyclic antidepressants – but not other classes of antidepressants – were also associated with substantial HRV reductions, findings associated with a large effect size (Hedges' g = -1.24). In a more recent study (Kemp et al., n.d.), the effects of SSRIs have been shown to be heterogeneous, such that users of paroxetine display HRV reductions relative to other users of SSRIs, while fluoxetine was the only SSRI no associated with HRV reductions.

The meta-analysis on anxiety disorders (Chalmers et al., 2014) was conducted on a total of 2,086 patients and 2,294 controls. Like the meta-analysis conducted on MDD, this study was conducted because prior studies had reported inconsistent findings, again, highlighting the need for an

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

In the largest independent cohort to date (N=15,105), we reported that use of antidepressant medications is associated with robust increases in heart rate and decreases in its variability (d's ranged from 0.37-0.95) (Kemp, Brunoni, et al., 2014a). However, we also observed that generalised anxiety disorder displays replicable, albeit small, reductions in vagal activity after controlling for multiple confounding variables, including medication use. This study was unique in that it capitalized on propensity score matching procedures, which have several advantages over ANCOVA and traditional regression-based techniques including reduced bias by estimating propensity scores without reference to the outcome variable (i.e. HRV) (McCaffrey et al., 2013). While it is notable that participants with depression did not display reductions in vagal activity in this analysis, this study has since been extended (Kemp, Brunoni, et al., 2014a), and new findings indicate that patients with melancholia (n=40) display robust alterations in resting state heart rate and its variability (measured by resting state time-, frequency- and non-linear domain measures), relative to controls (n=94). These findings were associated with a moderate effect size (d's = 0.56–0.58) and highlight the important impact of disorder heterogeneity.

It is also important to realize that MDD and anxiety are frequently comorbid conditions: MDD has high-comorbidities with the whole range of anxiety disorders (Goldberg & Fawcett, 2012). Correlations range from 0.62 for generalized anxiety disorder, 0.52 for agoraphobia and social

phobia, 0.48 for panic disorder and 0.42 for obsessive compulsive disorder (Goldberg & Fawcett, 2012). The close relationship between MDD and generalized anxiety disorder in particular, is thought to relate to shared symptoms – especially negative affect – and genetic risk factors (Goldberg & Fawcett, 2012). It is also relevant therefore that MDD patients with comorbid generalized anxiety disorder have been shown to display the most robust reductions in HRV (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012a). These findings may relate to patients inability to disengage from threat detection, even in the absence of any real threat (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012a; Thayer & Lane, 2000). This behavioral characteristic may be underpinned by prolonged prefrontal inactivity, disinhibition of the central nucleus of the amygdala, and activation of medullary cardioacceleratory circuits (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012a; Thayer et al., 2009).

The mood and anxiety disorders themselves, are often comorbid with alcohol dependence (e.g. Merikangas et al., 1998), a condition that has also been associated with a body of contradictory evidence. A large study on 2,947 participants from the NESDA cohort (Boschloo et al., 2011) had reported that alcohol use, but not its dependence, is associated with dysregulation of the hypothalamic-pituitary-adrenal axis and the ANS. Critically however, heavy drinkers only displayed an increased heart rate, but no decreases in HRV, as measured by RSA. However, the more recent meta-analysis on patients with alcohol dependence (n=177) (Quintana, McGregor, Guastella, Malhi, & Kemp, 2013c) observed a lowered HRV in this patient group (relative to non-dependent individuals, n=216), a finding associated with a medium effect size (Hedges' g = -0.6). Importantly, inclusion of the data reported by Boschloo and colleagues (Boschloo et al., 2011) did not change the conclusions drawn in the meta-analysis (Quintana, McGregor, Guastella, Malhi, & Kemp, 2013c). Also, findings were not dependent on comorbid psychiatric disorders. It was concluded that lowered HRV in alcohol dependence may underpin some of the behavioral features of the disorder including social dysfunction (Monnot, Nixon, Lovallo, & Ross, 2001) and impulse control (Ingjaldsson, Laberg, & Thayer, 2003).

While alcohol dependence are associated with HRV reductions, moderate, habitual drinking (n=25) – classified according to a score of between 2 and 5 on the Alcohol Use Disorder Identification Test Consumption subscale (AUDIT-C) corresponding to ~1 standard drink, 5 days a week – is associated with an increase in resting-state, vagal activity (HF-HRV), relative to nonhabitual drinkers (n=22) (d = 0.65) (Quintana, Guastella, McGregor, Hickie, & Kemp, 2013a). Epidemiological studies indicate that the relationship between alcohol consumption and health

outcomes reflects a J-shaped curve (Corrao, Bagnardi, Zambon, & La Vecchia, 2004; Elkind et al., 2006; Hvidtfeldt et al., 2010; Stampfer, Colditz, Willett, Speizer, & Hennekens, 1988): moderate alcohol consumption confers a protective effect, relative to abstinence, while heavy consumption and dependence is associated with poorer health. For example, a meta-analysis on 156 studies of 15 diseases (N=116,702) reported a minimum risk ratio 0.80 for coronary heart disease at 20 g/day indicating a significant protective effect, which was observed up to 72 g/day, while increased risk was obtained from 89 g/day (RR > 1.05) (Corrao et al., 2004). We (Quintana, Guastella, McGregor, Hickie, & Kemp, 2013a) have previously proposed that resting (tonic) vagal activity may provide a candidate psychophysiological marker for the findings reported in the epidemiological literature.

Our meta-analysis on schizophrenia (Clamor et al., 2016) was conducted to determine the robustness and size of the effect that had been reported in prior studies. While HRV decreases had been reported, there was considerable heterogeneity in the HRV indices that had been selected, the type of participants recruited in studies and in the results that had been reported. A meta-analysis was conducted on large samples of participants and a large effect size across studies was confirmed for both RMSSD (N= 2,485; Hedges' g = -0.91) and HF-HRV (N= 3,055; Hedges' g = -0.98), and the effect persisted even when studies that could have been impacted on by bias were excluded from analysis. HRV alterations were also examined across different sub-groups of the disorder, including first-episode, chronic, acute inpatient, stable outpatient as well as medicated and unmedicated participants, emphasizing the robustness of the results. This study concluded that low HRV in schizophrenia may actually reflect an endophenotype of the disorder. HRV reflects prefrontal cognitive function, and schizophrenia displays complex executive dysfunction (Neill & Rossell, 2013). HRV also reflects capacity for emotion perception and its regulation, and schizophrenia also displays difficulties in emotion regulation (Lincoln, Hartmann, Köther, & Moritz, 2015). Finally, brain regions in which activity has been associated with HRV such as anterior cingulate cortex and medial prefrontal cortex, have also been implicated in the development of schizophrenia (Shepherd, Laurens, Matheson, Carr, & Green, 2012). While the large effect size associated with the finding is striking, and this effect is greater than that observed for the mood and anxiety disorders, direct comparisons across disorders are rare and inconclusive (e.g. Moon, Lee, Kim, & Hwang, 2013), highlighting an important area for future research.

As for schizophrenia, borderline personality disorder (BPD) is also associated with emotion dysregulation and is characterised by high rates of comorbidity with mood and anxiety disorders, and substance abuse disorders. However, only two of the 5 studies suitable for meta-analysis

actually reported statistically significant differences between BPD participants and controls. The meta-analysis on BPD (Koenig et al., 2016) therefore sought to quantify the evidence for alterations in resting state HRV, relative to healthy controls (N=200). A reduction in resting-state HRV was confirmed, a finding associated with a medium effect size (Hedges' g = -0.59), highlighting the utility of meta-analysis over individual studies, which often lack statistical power. This meta-analysis concluded that low HRV may reflect an important trait characteristic of BPD, underpinning difficulties in emotion regulation and impulsivity.

In addition to HRV reductions during the presence of the disorder, we note that studies have also observed HRV reductions during euthymia (Braeken et al., 2013; Brunoni et al., 2013; H. A. Chang et al., 2013b). These findings suggest that vagal impairment may actually persist despite successful treatment, perhaps providing a psychophysiological mechanism for the observation that previously depressed individuals are more vulnerable to future episodes of depression, a phenomenon known as 'kindling' (Post, 1992). While it is possible that these persistent reductions in HRV relate to the impact of medications including antidepressants (Kemp et al., 2010; Kemp, Brunoni, et al., 2014a; Licht, de Geus, van Dyck, & Penninx, 2010) and medications with anticholinergic effects (often prescribed for hypertension and cardiovascular disease) we recently demonstrated that unmedicated women with a history of – but not current – anxiety disorders display decreased HRV (RMSSD d = 0.58; HF-HRV d = 0.72) (Braeken et al., 2013). Strikingly, we also observed (Braeken et al., 2013) that 2-4 month old offspring of pregnant women with a past history – but not current – anxiety also display HRV reductions (RMSSD d = 0.63; HF-HRV d = 0.63). These decreases in HRV at 2-4 months of age also predicted fearful behaviour at 9-10 months of age, pointing to possible underlying mechanisms of future psychopathology. In another study (Brunoni et al., 2013) HRV did not change following treatment with either a non-pharmacological (transcranial direct current stimulation) or pharmacological (sertraline) intervention, nor did HRV increase with clinical response to either treatment. Another study on an unmedicated, physically healthy sample (H. A. Chang et al., 2013b) observed that while HRV resolved in patients with fully remitted MDD, autonomic dysregulation was still observed in those remitted patients with a history of suicidal ideation. Further study on the potential of other non-pharmacological therapies (e.g. psychological therapies, exercise, meditation and HRVB) to normalize vagal impairment will likely have major public health significance.

In addition to health behaviours such as exercise and meditation (see previous sections), it is worth noting research interest in applying HRV biofeedback (or HRVB) in the treatment of a variety of

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

Summary

These findings highlight that low HRV is displayed in a wide range of psychiatric disorders and have led us to propose HF-HRV as an autonomic, transdiagnostic biomarker of mental illness (Beauchaine & Thayer, 2015). This impairment in vagal function may contribute to some of the characteristic features (e.g. emotion dysregulation) commonly observed across these disorders. Critically, vagal impairment often does not improve with amelioration of symptoms, and this impairment may even impact on the offspring of mothers with prior psychiatric illness (Braeken et al., 2013), highlighting the need for further studies to identify treatment options to normalize vagal function in these populations. The long-term consequences of reduced vagal function on physical health are the issues we turn our attention to next.

Vagal Function and Physical Health

Research has highlighted an intimate relationship between psychological and physical wellbeing, and vagal function may provide a structural link (see Kemp & Quintana, 2013 for review). Meta-analysis on 35 studies investigating mortality in initially healthy populations (Chida & Steptoe, 2008) reported that positive psychological wellbeing is associated with reduced mortality in healthy individuals. Stronger protective effects were observed for studies of initially healthy populations with follow-ups of up to 10 years. Analyses of different causes of death revealed that wellbeing was associated with reduced all-cause mortality (19% reduction in hazard ratio) and cardiovascular mortality (29% reduction). Importantly, these findings are based on multivariate models with appropriate adjustment for potential confounding factors. By contrast, a study on more than 65,000 people from the general population who were free from cardiovascular disease and cancer at baseline reported that psychological distress increases risk of mortality in a dose-response pattern by up to 94% over 8 years (Russ et al., 2012). Again findings remained highly significant even after controlling for important behavioural and lifestyle factors. Finally, a recently published meta-review on 20 different mental disorders in over 1.7 million patients reported that all disorders have an increased risk of all-cause mortality, relative to the general population. Strikingly, all major mental disorders were associated with reductions in life expectancy (7-24 years), which was similar to or greater than the effects of heavy smoking (8-10 years) (Chesney, Goodwin, & Fazel, 2014).

We and others have previously reviewed the literature on the role of vagal function in morbidity and mortality (Kemp & Quintana, 2013; Thayer, Yamamoto, & Brosschot, 2010c), and have suggested that chronic vagal impairment may have a ‘wear and tear’ effect on the human body (Verkuil, Brosschot, Gebhardt, & Thayer, 2010). These effects include increases in the electrical instability of the heart, platelet aggregability, coronary vasoconstriction and left-ventricular wall stress (P. J. Schwartz & Priori, 1990). A prospective study on 1933 participants aged 18 to 65 years from the Netherlands Study of Depression and Anxiety (NESDA) study, reported that ANS dysregulation predicts development of the metabolic syndrome (Licht, de Geus, & Penninx, 2013). ANS measures included heart rate, RSA, pre-ejection period (or PEP, a marker of noradrenergic ionotropic drive to the left ventricle such that shortened PEP reflects increases in sympathetic activity), cardiac autonomic balance (CAB) and cardiac autonomic regulation (CAR). The CAB and CAR indices provide two useful measures of autonomic balance (Berntson, Norman, Hawkley, & Cacioppo, 2008). High values on CAB reflect a favourable cardiac pattern of low sympathetic (indexed by PEP) and high vagal (RSA) cardiac activity, while low (high) values on CAR reflect coinhibition (coactivation) of the two cardiac branches. This study (Licht et al., 2013) defined metabolic syndrome by the Adult Treatment Panel III criteria (Grundy et al., 2005), which included

high waist circumference, serum triglycerides, blood pressure, serum glucose, and low high-density lipoprotein (HDL) cholesterol. Baseline quartiles of heart rate, PEP, CAB were associated with new onset of the metabolic syndrome among those without metabolic syndrome at baseline. Higher heart rate was associated with an increase in the odds for new onset of metabolic syndrome (OR=1.97), while higher PEP and CAB were associated with a decrease in the odds for new onset (OR = 0.46 and OR = 0.57, respectively). How might high CAB reduce odds for metabolic syndrome? Vagal function is known to play an important role in regulating the inflammatory reflex (Tracey & Pavlov, 2012), a neural mechanism involved in metabolic homeostasis and control of innate immune responses. In this regard, high CAB may reflect a healthy anti-inflammatory reflex (see Kemp & Quintana, 2013; Tracey & Pavlov, 2012 for reviews), contributing to better regulation of proinflammatory cytokine activity and protecting against other metabolic complications (Donath & Shoelson, 2011; Hotamisligil, 2006). Decreased HRV has been shown to precede elevated levels of inflammatory markers (Jarczok et al., 2014), thus, interventions that increase HRV may have positive effects on diseases of inflammation and metabolic syndrome via downstream pathways including the SNS.

Short-term, resting and ambulatory measures of HRV decrease with increasing age (Agelink et al., 2001; Jennings & Mack, 1984; Yeragani et al., 1997), and age is associated with increasing morbidity and mortality, highlighting age as an important confounding variable in studies exploring associations between vagal function, morbidity and mortality. Cross-sectional research on 344 healthy participants ranging from 10 to 99 years of age (Zulfiqar, Jurivich, Gao, & Singer, 2010) highlighted that HRV (RMSSD, pNN50) – extracted from 24-hour ambulatory Holter recordings – decreases rapidly from the second to fifth decades (r = -0.58), this decrease then reaches a nadir in the 8th decade, after which a significant, progressive increase to higher levels is observed. At the nadir, RMSSD had decreased 64% and pNN50 88% from the second-decade baseline values, while the tenth decade was characterised by increases in RMSSD and pNN50 of 58% and 233% respectively, characteristic of values obtained during the fifth-decade. It is possible that this latter increase reflects a survival bias, such that older participants with low HRV may have already died before the study was conducted, leading to an artificial increase in HRV following the 8th decade. Even so, findings still highlight the tight connection between vagal function, ageing and longevity. The authors themselves concluded that persistently high HRV in the elderly is predictive of longevity.

Research has typically focused on populations with current cardiovascular disease, and examined the capacity for HRV to predict future adverse events (see Carney & Freedland, 2009 for a review) (see also Bigger et al., 1988; Huikuri & Mahaux, 2003; Karp et al., 2009). Findings indicate that HRV accounts for a substantial part of the risk associated with depression in CHD. For example, a study on 311 depressed patients with a recent acute myocardial infarction recruited for the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study (Carney et al., 2005), reported that depressed patients remained at a higher risk for all-cause mortality over a 30-month follow-up period (hazard ratio: 2.8) after adjusting for potential confounders. The authors reported that reduced very low frequency HRV based on 24-hour ambulatory Holter recordings accounted for one-quarter of the mortality risk relating to depression. Another prospective study (Carpeggiani, 2005) that followed 246 patients after myocardial infarction reported that personality traits including low emotional insensitivity and insecurity, as well as reduced HF-HRV – measured using 24-h Holter monitoring – predicted increased risk for cardiac mortality (relative risk = 4.18 and 2.76, respectively) up to 8-years following initial event. Low emotional sensitivity reflects social inhibition and an inability to express emotion, a characteristic that may be associated with reduced HRV itself (as discussed above). This restricted capacity to express emotion may lead to chronic distress, which will further contribute to impairment in vagal function. Importantly, participants in this study did not have a history of psychiatric illness, nor were they on psychotropic medications.

A study in mice (Norman et al., 2012) sought to better understand what mechanisms might underpin the increase in morbidity and mortality following myocardial infarction. This study randomly assigned animals to two experimental groups: normothermic cardiac arrest (n=12) or hypothermic cardiac arrest (as a control group, n=10). Cardiac arrest was induced through injection of potassium chloride via a jugular catheter, and this was followed by injection of epinephreine and chest compressions. The heads of controls were maintained at 27°C to prevent neurological damage. HF-HRV was observed to decrease rapidly 24h after experimentally induced cardiac arrest, and these decreases were correlated with neuronal damage and microglial activation in hippocampus by day 7. This study provides important clues in regards to the physiological consequences of cardiac arrest resulting from cessation of blood flow to the brain (global cerebral ischemia), and suggests that low HRV may provide a marker of subsequent brain damage. The authors note that the hippocampus is one of the more susceptible regions of the brain to ischemic damage, that this region directly innervates structures within the CAN, and that stimulation of this region is associated with decreases in heart and respiration rate. While the authors acknowledge that the study was not able to determine a causal relationship between neuroinflammation and vagal function, their findings

indicate that vagal function following cardiac arrest may provide an index of susceptibility to neuronal damage.

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

Similarly, meta-analysis has reported that HRV – based on a variety of measures extracted from short- and long-term recordings – predicts first cardiovascular event in individuals without known cardiovascular disease over a period of 3.5 to 15 years (mean follow-up duration of included

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

Summary

In summary, studies have highlighted a key role for vagal function in longevity and its impairment as a causal factor in morbidity and mortality. We highlight two major findings: (1) vagal function has important long-term consequences for future health and wellbeing after addressing multiple confounding factors, and (2) impairment in vagal function predicts cardiovascular and all-cause mortality in those with *and* without cardiovascular disease at baseline. We now synthesise the body of literature reviewed above, and present a model that attempts to bridge the gap from everyday psychological moments to mortality.

A Synthesis and Model

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

INSERT FIGURE 3 ABOUT HERE

Our model explicitly recognises bidirectional relationships between vagal function and psychological moments, which over time will contribute to physical disease (wellbeing) and mortality (longevity). Our model also draws on evidence (Kok et al., 2013; Kok & Fredrickson, 2010) that highlights mutual causation between psychological moments and vagal function, such that increases (decreases) in function will reciprocally and prospectively predict each other in an upward (downward) spiral of reciprocal causality. Vagal nerve outflow and connections with other cranial nerves will contribute to the capacity for social engagement, impairment on which is a core characteristic of the psychiatric disorders (Porges, 2011; Quintana, Kemp, Alvares, & Guastella, 2013b). The mood and anxiety disorders without cardiovascular disease display impaired vagal function (Kemp et al., 2010; Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012a), which may subsequently trigger the inflammatory cascade (Kiecolt-Glaser et al., 2002) and allostatic load (Danese & McEwen, 2012; McEwen, 1998) leading to morbidity and mortality. On the other hand, physical disease may also contribute to the development of psychiatric illness. Recent population-based, prospective cohort studies – on 3.56 million people with more than 77 million person-years of follow-up (Benros et al., 2011; 2013) – show for example, that hospitalisation for autoimmune diseases and severe infection increase the risk for schizophrenia and mood disorders in a dose-response relationship.

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

Summary

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

Theoretical Conundrums & Methodological Limitations

The body of research reviewed above provides considerable evidence on which our proposal is based: that vagal function may provide the missing structural link between everyday psychological moments and mortality. People's reactions to everyday moments both affect and are affected by the vagus in ways that have long-term effects on mortality. However, the literature is also characterised by a variety of theoretical conundrums and contradictory findings. We briefly review and comment

on some examples below, an effort we hope will motivate and inspire future studies to further explore some of the issues raised, bearing in mind the various methodological limitations noted.

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

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

Thirdly, other lines of evidence indicate that high levels of vagal function may be observed in individuals at risk of mania (Gruber, Johnson, Oveis, & Keltner, 2008) and in bipolar disorder (Gruber, Harvey, & Purcell, 2011). Participants characterised by high – relative to low risk – for mania, according to the Hypomanic Personality Scale (HPS) (Eckblad & Chapman, 1986), display elevated positive emotion and tonic vagal function (d = 0.53) at rest (based on a 90-sec pre-film

baseline when participants were completing questionnaires), as well as during presentation of positive, negative and neutral films (d = 0.47) (Gruber et al., 2008). Although this study was based on young adults (N=90), the HPS captures elevations in positive mood states and high-scorers on this measure have been shown to overlap with bipolar patients. Another study by these authors reported that patients with bipolar disorder (n=23) display smaller decreases in RSA – as determined by the peak-valley method – during emotion-eliciting films, compared to non-clinical controls (n=24) (d = 0.61) (Gruber et al., 2011). Interestingly, this study further reported that mean RSA levels (prior to computing change scores) were higher for bipolar patients compared to controls. Further research is needed on bipolar disorder, including investigating the impact of different phases of the illness within patients and in comparisons with other diagnostic groups, as well as meta-analysis, which may help to clarify the impact of this disorder on vagal function.

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

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Conclusions

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

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Summary

In summary, while the extant research provides a solid foundation on which we propose a key role for vagal function in the pathway from psychological moments to mortality, studies have also been

characterised by a variety of limitations, contradictory findings and interpretative issues, highlighting a need for continued study to further understand the relationship between everyday psychological moments and mortality. Further research is especially needed on how (mediation) and when (moderation) vagal function impacts on downstream pathways. While studies have typically emphasised the direct effects of downstream processes – such as insulin resistance and inflammatory processes – on cardiac function, research has only recently begun to account for the central effects on autonomic cardiovascular control (Harrison, Cooper, Voon, Miles, & Critchley, 2013; Ryan, Sheu, Verstynen, Onyewuenyi, & Gianaros, 2013)

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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 cardioaccelleratory 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.

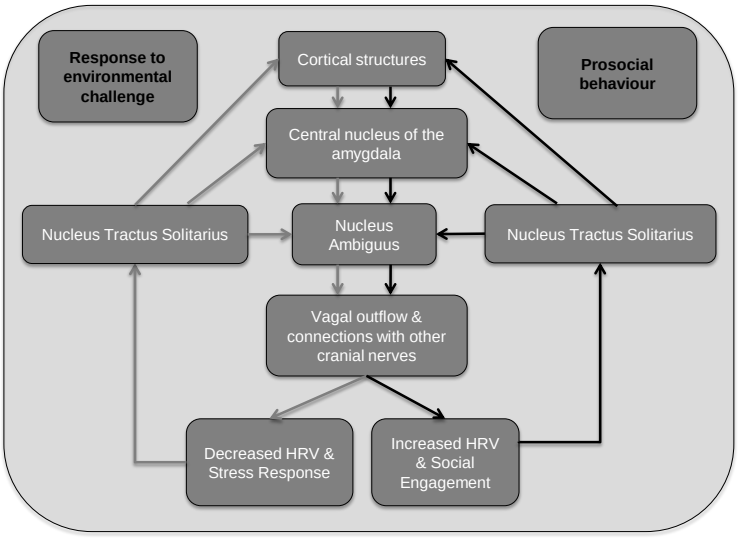

Fig 2: Example of a participant's RR-interval trace as graphed in Kubios software. Higher values on the vertical RR axis indicate slower heart rate, and variability in the trace is indicative of HRV. During rest, heart rate is characterised by slower heart rate and a high level of HRV. The stress task 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.

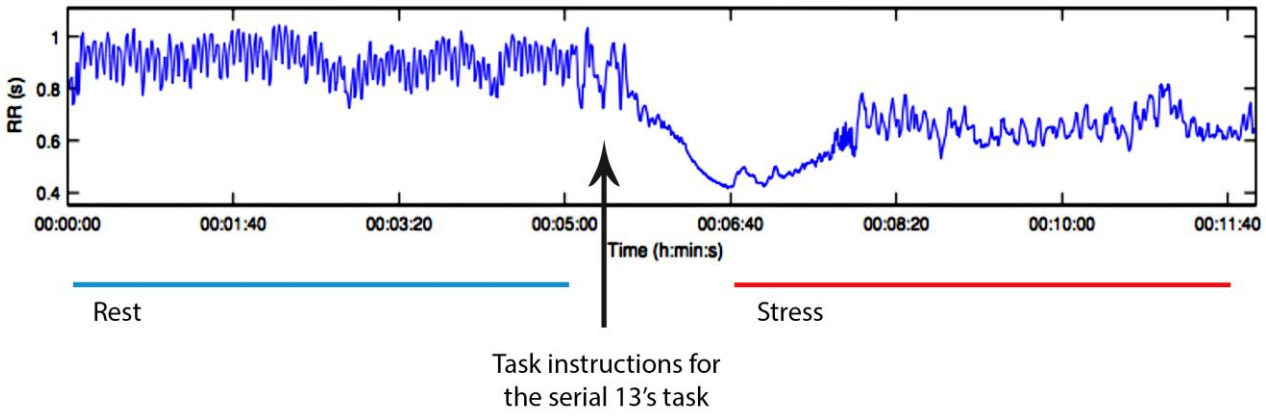

Fig 3. Neurovisceral Integration Across a Continuum of Time (NIACT) characterising the link between psychological moments to mortality: the extent of neurovisceral integration is dependent on vagal functioning and underpins experience of psychological moments (Fig 1). Impaired vagal function leads to 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).

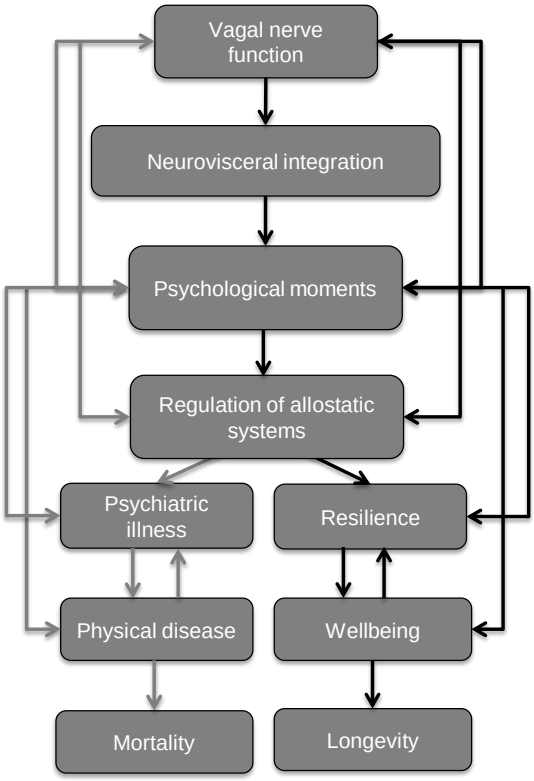

Table 1: Summary of common HRV parameters and their interpretation.

Measure	Units	Interpretation
Time Domain		Measures of variance calculated on NN intervals (cleaned R-R time-series) to yield numerical estimates in temporal units (milliseconds, ms).
MeanRR	ms	The mean of NN intervals; the longer the NN interval, the slower the heart rate (more HRV). Conversely, the shorter the RR interval, the faster the heart rate (less HRV). Higher resting heart rate and lower resting HRV usually reflect a compromised physiological state.
SDNN	ms	The standard deviation of NN intervals reflects all cyclic components responsible for variability during an entire recording. 24-hour recordings reflect circadian influences and total HRV, such that higher values reflect a healthier state, while lower values are associated with increased risk of mortality, especially in patient populations.
RMSSD	ms	Square root of the mean squared differences between successive RR intervals. This measure correlates highly with HF-HRV and reflects beat-to-beat changes mediated by the SNS. RMSSD is less affected by changes in breathing frequency than for the HF component.
pNN50	%	NN50 divided by the total number of RR intervals. Provides information about the very short-term control of subtle 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 the ebb and flow of heart rate associated with respiration. RSA can be quantified using spectral analysis, time-domain peak-valley analysis or application of a band-pass filter, so units of measurement can vary.
Frequency Domain		Variance in heart rate is partitioned into frequency spectra using various approaches, the most common being fast Fourier transform (FFT) and autoregressive modelling techniques.
High Frequency		HF corresponds to heart rate variations in the respiratory cycle (0.15 and 0.40 Hz). Reflects vagal activity such that

(HF)		higher values. Total vagal blockade eliminates oscillations in this frequency range.
HF-HRV(n.u.)	n.u.	HF [ms2]/(total power [ms2] − VLF [ms2]). This measure minimizes the effects of total power on HF values. Increases in normalised HF can be driven either by increases in overall HF power or by decreases in LF power.
HF-HRV(ms^2)	ms^2	Reflects parasympathetic activity, although dependent on total power. Total power is decreased with sympathetic activity (e.g. tachycardia) and increased with vagal activation, highlighting the importance of task context when interpreting results.
LF-HRV		LF may also be presented in normalised units [nu] and absolute power [ms2]. Interpretation of activity in the LF band (0.04–0.15 Hz) is controversial and depends on the recording condition in which data is collected; it can reflect vagal, sympathetic and baroreflex mechanisms.
Non-Linear		Non-linear measures assess qualitative properties rather than magnitude of heart rate dynamics. Such measures may be more sensitive to group differences, however, the physiological basis of these measures is less clear.
The Poincaré plot		A geometrical technique that involves fitting an ellipse to the shape of the N-N interval time-series to extract three indices: SD1, SD2, and SD1/SD2.
SD1	ms^2	The minor axis of the Poincare plot ellipse is a measure of rapid changes in the N-N interval and is therefore considered a parasympathetic index of sinus node control. Correlates highly with RMSSD and HF measures.
SD2	ms^2	The major axis of the Poincare plot ellipse is a measure of long-term variability.
SD1/SD2		The ratio between the two standard deviations of the Poincaré plot. SD1/SD2 ratio has fractal-like properties, information that is otherwise hidden from time- and linear-domain measures of HRV.
Recurrence plot quantification		The tool quantifies the degree of determinism, state changes and degree of complexity and/or randomness in cardiac signals and requires no mathematical transformations or assumptions. Higher values on measures extracted from the recurrence plot quantification include % REC, Lmax and Lmean. These variables reflect a pattern of low variability, and

		a compromised physiological state.
Entropy		Entropy reflects the regularity or periodicity of time series; higher regularity is reflected in lower values.
ApEn		Approximate entropy quantifies the regularity of the R-R time series, such that the more regular and predictable the time series, the lower the value. This measure has three shortcomings including dependence on record length and lack of relative consistency, leading to an alternative measure, SampEn.
SampEn		A lower value of sample entropy indicates more self-similarity in the time series.
EntShannon		Shannon entropy is another measure of pattern distribution complexity that is large when the distribution is flat, and small if there is a probable subset of patterns, while others are missing or infrequent (a Gaussian distribution). This measure therefore is interpreted differently to ApEn and SampEn.
DFA		Discriminatory Function Analysis quantifies intrinsic fractal-like correlation properties of dynamic systems.
DFA1		Short-term fluctuations of DFA reflects the short-term, fractal-like properties of rapid R-R interval oscillations (for window sizes < 11 beats). White Gaussian noise (a totally random signal) is reflected in a value of 0.5; a Brownian noise signal (a signal in which higher frequencies display decreased power) is reflected in a value of 1.5. Healthy middle-aged subjects display values around 1.0.
DFA2		Long-term fluctuations of DFA reflect longer term, fractal-like scaling properties (for window sizes > 11 beats).
CorrDimD2		The correlation dimension quantifies the complexity or ‘strangeness’ of data, providing information on the minimum number of dynamic variables needed to model the underlying system