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Heart rate and autonomic response to stress after experimental induction of worry versus relaxation in healthy, high-worry, and generalized anxiety disorder individuals

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ABSTRACT

Generalized anxiety disorder (GAD) is the most commonly occurring anxiety disorder and has been related to cardiovascular morbidity such as cardiac ischemia, sudden cardiac death, and myocardial infarction. Both GAD and its cardinal symptom – worry – have been shown to promote muted physiological reactivity in response to laboratory and ecological stressors. Importantly, no study to date has examined the concurrent and relative contributions of trait and state worry within healthy controls, (non-clinical) high trait-worry controls, and GAD participants. The present study examined heart rate (HR), respiratory sinus arrhythmia (RSA), and salivary alpha-amylase (sAA) responses to laboratory stress during and following the experimental induction of worry versus relaxation in healthy controls ($n = 42$), high trait worriers ($n = 33$) and participants with GAD ($n = 76$). All groups exhibited increased HR and decreased RSA in response to the stressor, with no differences by condition. Baseline sAA significantly moderated HR and RSA reactivity, such that higher sAA predicted greater increases in HR and decreases in RSA. There was a significant group by baseline sAA interaction such that in GAD, higher baseline sAA predicted decreased change in sAA during stress, whereas higher baseline sAA predicted greater sAA change in healthy controls. High-worry controls fell non-significantly between these groups. The present study provides additional evidence for the effect of worry on diminished HR stress response and points to possible suppression of adrenergic sympathetic stress responses in GAD.

1. Introduction

Generalized anxiety disorder (GAD) is the most commonly occurring anxiety disorder and one of the most highly co-occurring disorders in the diagnostic and statistical manual of mental disorders-fourth edition (DSM-IV; Kessler et al., 2005; Maier et al., 2000). A chronic and disabling disorder, GAD is associated with substantial personal, societal, and economic costs (Ballenger et al., 2001; Wittchen, 2002). Moreover, GAD has been associated with cardiovascular disease such as cardiac ischemia, sudden cardiac death, and myocardial infarction (Frasure-Smith and Lesperance, 2008; Martens et al., 2010). Evidence points to physiologic rigidity in GAD that limits or inhibits normative responses to environmental demands (Hoehn-Saric and McLeod, 2000). This pattern of rigid or reduced responding has been termed diminished physiological flexibility (c.f. Hoehn-Saric et al., 2004), and refers to an absence of expected variability in physiological indices such as heart rate (HR) and respiratory sinus arrhythmia (RSA). A lack of flexibility in regulatory capacity is potentially problematic, as rigidity in physiological systems has been related to mortality and physical morbidity (Lipsitz and Goldberger, 1992; Peng et al., 1994).

In one of the first studies to examine the role of the autonomic nervous system (ANS) in GAD, 20 females with GAD exhibited narrower ranges of HR than did controls in response to two laboratory stressors (Hoehn-Saric et al., 1989). Thayer and colleagues hypothesized that these effects were mediated by poor parasympathetic regulatory tone and in two separate studies demonstrated that individuals with GAD exhibited both lower levels of RSA–a proxy for parasympathetic control of HR–at baseline as well as invariant parasympathetic responses to laboratory stressors (Lyonfields et al., 1995; Thayer et al., 1996). Likewise, in an ecological assessment of these effects, persons with GAD exhibited lesser RSA compared to controls over the course of a 4-day ambulatory study (Hoehn-Saric et al., 2004). Finally, Fisher et al. (2010) found evidence for diminished stress reactivity in adrenergic sympathetic arousal in GAD participants versus controls in response to a laboratory stressor. Taken together these studies demonstrate that, across measurements of the ANS and within both laboratory and ecological settings, persons with GAD exhibit diminished physiological reactivity following stressors.

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Of note, worry – the cardinal feature of the current diagnostic criteria for GAD – has been similarly related to diminished stress reactivity (c.f. Borkovec and Hu, 1990). Brosschot et al. (2006) have implicated perseverative cognition – which subsumes worry and the related construct, rumination – as a potential causal mechanism in negative health outcomes. Worrisome thinking prior to exposure to phobic imagery has been shown to dampen cardiovascular response in anxious individuals (Borkovec and Hu, 1990; Borkovec et al., 1993; Llera and Newman, 2010) and laboratory inductions of worry have likewise been shown to lead to reduced RSA in nonanxious controls (Lyonfields et al., 1995; Thayer et al., 1996). Worry generated higher HR and lower RSA when compared to a resting baseline in 43 healthy males (Hofmann et al., 2005), as well as when compared to relaxation in 53 healthy adults of mixed gender (Verkuil et al., 2009). Finally, in a 24-h ambulatory study of 52 healthy individuals, worry frequency predicted higher HR and lower RSA during waking, and worry duration predicted lesser RSA during both waking and sleeping (Brosschot et al., 2007). Taken together, these studies suggest a possible causal association between worrisome thinking and ANS impairment, most notably reduced parasympathetic cardiac control and increased HR.

Autonomic nervous system control of HR is vital to cardiovascular health. During periods of relative physiologic quiescence, heart rate is chronically inhibited by efferent parasympathetic nervous system (PNS) signals at the sinoatrial node.[1] These inhibitory signals are necessary for cardiac stability and flexibility and dysregulation of these effects has been shown to limit appropriate cardiac responsiveness (Levy, 1990; Verrier, 1987). Moreover, diminished vagally mediated RSA has been shown to predict congestive heart failure and hypertension (Curtis and O'Keefe, 2002) and has been used as a proxy for cardiovascular disease altogether (Stys and Stys, 1998). Low tonic RSA likewise has been shown to be a significant risk factor for all-cause mortality (Tsuji et al., 1994), whereas survival after myocardial infarction is positively related to greater levels of RSA (Stein et al., 1994). Therefore, it may be critical to distinguish the degree to which impaired RSA and PNS functioning are implicated in the process of worry and clinically diagnosed GAD.

However, autonomic control of HR is not limited to PNS influence. The primary source of increased cardiovascular reactivity during stress is drawn from increased sympathetic nervous system (SNS) activity (Hjemdahl et al., 1989), as the SNS predominantly regulates changes in HR during periods of increased metabolic demand. Moreover, Berntson et al. (1991) have demonstrated that the traditional doctrine of autonomic reciprocity, in which autonomic functioning lies along a single continuum from sympathetic to parasympathetic control, is insufficient for representing the ANS and that a two-dimensional space is required, at minimum. Thus, estimations of autonomic functioning should include concurrent measurement of the SNS and PNS when possible. In the case of GAD it may be crucial to understand the role of the SNS in the symptomatology and phenomenology of the disorder. Despite the removal of sympathetic arousal symptoms from the diagnostic criteria for GAD in the DSM-IV, Fisher et al. (2010) recently demonstrated that these symptoms are significantly elevated in at least a subset of the GAD population and that the severity of such symptoms is directly related to concurrent elevations in adrenergic sympathetic tone. Indeed, Curtis and O'Keefe (2002) assert that elevated HR and reduced HRV – two physiological conditions regularly reported in GAD – are chiefly the result of chronic and excessive sympathetic tone. Thus, not only is the examination of sympathetic tone in GAD indicated, but so too is the assessment of the relative behavior of SNS and PNS indices in relation to HR.

Unfortunately, the delineation of the specific causal factors underlying diminished physiological flexibility in GAD has been confounded by the use of persons with GAD, non-clinical samples stratified by level of trait anxiety or trait worry, and general populations in worried states. This conflation of disparate populations likely belies differences in the amount, duration, severity, and function of worry within each group. Thus, the utilization of methodologies such as high trait-worry control groups, experimental inductions of worry, and momentary assessments of phasic worry may help to identify whether the construct of worry or the greater clinical syndrome of GAD is responsible for the rigidity previously observed in autonomic stress reactivity. Given the often synonymous treatment of worry and GAD in the literature (c.f. Brown et al., 1998) it is important to investigate whether the phenomenon of chronic worry is responsible for the diminished physiological flexibility demonstrated in GAD, or if the greater clinical syndrome is required to observe significant effects. This is an important distinction to make given that worry has been implicated in nearly all mood and anxiety disorders (Barlow, 2004; Brosschot et al., 2006).

Several authors have argued that worry is a mediator, rather than a moderator of the effects of psychological and psychosocial stressors on long-term health (Brosschot et al., 2006, 2007; Thayer and Lane, 2002). Within this model worry perpetuates the effects of passing stressors by maintaining the cognitive representation and thereby the physiological presence of the stressor, prolonging the impact of that stressor on the body. Such an argument would seem to support the hypothesis that worry and not the larger clinical syndrome of GAD is the causal mechanism in the diminished physiological flexibility observed in GAD. Consistent with this hypothesis, Kubzansky et al. (1997) demonstrated that worry proneness predicted a second myocardial infarction. However, no work to date has compared clinically diagnosed GAD and non-clinical, high-trait-worry populations directly. This is a potentially vital distinction to be drawn given that Martens et al. (2010) found that the presence of GAD predicted a 62% higher rate of negative cardiovascular outcomes, and this effect was not affected by the presence of comorbid psychological disorders. Thus, despite the prevalence of worry across the general population and within multiple DSM disorders, the broader clinical syndrome of GAD may make an independent contribution to poor cardiovascular health.

The present study utilized a healthy control group, a clinically diagnosed GAD group, and a high-worry control group (HW), with significant elevations in trait worry and no Axis I diagnoses. In order to control for and test against the influence of phasic worry, an experimental manipulation was additionally employed whereby all study participants were randomly selected to receive a worry or relaxation induction prior to the presentation of laboratory stressors[2] and levels of phasic worry were measured at four points throughout the study. Thus, the present study employed a 3×2 design to test the comparative effects of state and trait worry and clinically diagnosed GAD on physiological flexibility. The flexibility versus rigidity of the ANS-regulated cardiac response to stress was measured via HR, RSA and the sympathetic marker salivary alpha-amylase (sAA; see Section 2). Heart rate and RSA were measured across an initial baseline, experimental induction of worry versus relaxation, and two iterations of a

[1] The level of inhibitory control is often referred to as vagal tone, in reference to the vagus nerve (cranial nerve X), which innervates the viscera. RSA has been proposed as a measurable proxy for vagal tone (Porges, 1995).

[2] A potentially important methodological inclusion as Llera and Newman (2010) found that not only did worry elicit lesser RSA in GAD analogues, the induction of worry prior to the presentation of fearful material dampened robust parasympathetic withdrawal in response to the feared stimulus.