Sympathetic and hypothalamic-pituitary-adrenal asymmetry in generalized anxiety disorder

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Abstract

Physiologic investigations of generalized anxiety disorder (GAD) have skewed toward assessment of the autonomic nervous system, largely neglecting hypothalamic-pituitary-adrenal (HPA) axis variables. Although these systems coordinate—suggesting a degree of symmetry—to promote adaptive functioning, most studies opt to monitor either one system or the other. Using a ratio of salivary alpha-amylase (sAA) over salivary cortisol, the present study examined symmetry between the sympathetic nervous system (SNS) and HPA axis in individuals with GAD (n = 71) and healthy controls (n = 37). Compared to healthy controls, individuals with GAD exhibited greater baseline ratios of sAA/cortisol and smaller ratios of sAA/cortisol following a mental arithmetic challenge. We propose that the present study provides evidence for SNS-HPA asymmetry in GAD. Further, these results suggest that increased SNS suppression in GAD may be partially mediated by cortisol activity.

Descriptors: Generalized anxiety disorder, Cortisol, Salivary alpha-amylase, Asymmetry

In the United States alone, generalized anxiety disorder (GAD) is a prevalent and highly co-occurring anxiety disorder (Kessler, Chiu, Demler, & Walters, 2005). Although chronic physiologic hyperarousal has historically been considered a hallmark feature of anxiety disorders, evidence suggests that this does not reliably extend to GAD (Hoehn-Saric, McLeod, & Zimmerli, 1989). Instead, prior findings suggest that GAD is characterized by diminished physiologic flexibility—that is, lesser variability—both at rest and in response to stressors (Fisher & Newman, 2013). However, within the GAD literature, data have skewed heavily toward assessment of the autonomic nervous system (ANS), resulting in comparably fewer studies of hypothalamic-pituitary-adrenal (HPA) axis activity (Mantella et al., 2008). Given the role of the HPA axis in adaptive physiologic functioning (Sapolsky, Romero, & Munck, 2000), it is equally important to understand HPA, as opposed to solely autonomic, functioning in GAD.

Pathological worry, the cardinal symptom of GAD, elicits significant subjective distress and, as such, may repeatedly stimulate the HPA axis. It has therefore been proposed that GAD may be characterized by HPA axis dysregulation (Mantella et al., 2008). However, to date, investigations of HPA axis activity in GAD have been equivocal (for a review, see Hilbert, Lueken, & Beesdo-Baum, 2014). In light of the permissive and suppressive effects of the HPA axis (Sapolsky et al., 2000), potential HPA abnormalities associated with GAD may be better clarified in the context of HPA axis regulation of, or interaction with, other physiological systems, namely, the ANS. Further, although both ANS—specifically, sympathetic nervous system (SNS)—and HPA effects independently contribute to the physiological stress response, most studies opt to exclusively monitor one system or the other (Schumacher, Kirschbaum, Fydrich, & Strohle, 2013). Given the association between these systems, Schumacher and colleagues note that a degree of coordination, or symmetry, should be expected. However, few studies have directly investigated SNS-HPA symmetry or its relation to maladaptive behavior (Schumacher et al., 2013).

Of the studies that have investigated SNS-HPA symmetry and its effects, a majority have focused on children and adolescents (Schumacher et al., 2013). Contrary to the view that joint SNS-HPA activation (i.e., increased symmetry) may result in excessive arousal and maladaptive behavioral outcomes, Bauer, Quas, and Boyce (2002) hypothesized that greater SNS-HPA asymmetry increases risk for childhood behavior problems. These authors note that these problems may be precursors to psychiatric disorders in adulthood. To date, empirical studies of this question have provided mixed results (Allwood, Handwerger, Kivilghan, Granger, & Stroud, 2011; El-Sheikh, Erath, Buckhalt, Granger, & Mize, 2008;
Fortunato, Dribin, Granger, & Buss, 2008; Gordis, Granger, Susman, & Trickett, 2008). For instance, whereas some have noted that greater SNS-HPA asymmetry is associated with externalizing and internalizing problems in children (El-Sheikh et al., 2008) and adolescents (Gordis et al., 2008), others have reported that greater SNS-HPA asymmetry is linked with these problems in youth (Allwood et al., 2011) and toddlers (Fortunato et al., 2008). To date, the relation between SNS-HPA symmetry and psychopathology in adulthood remains a largely understudied area (Bauer et al., 2002).

In addition to using salivary cortisol to index HPA axis activity (see Hellhammer, Wüst, & Kudielka, 2009, for a review), the few studies of SNS-HPA symmetry and its effects have largely used salivary alpha-amylase (sAA) to index SNS activity (cf. Allwood et al., 2011; El-Sheikh et al., 2008; Fortunato et al., 2008; Gordis et al., 2008). Salivary alpha-amylase is a noninvasive surrogate marker of central SNS activity that has recently garnered attention due to its ease of collection and relative sensitivity to stress-related stimuli (Granger, Kivlighan, El-Sheikh, Gordis, & Stroud, 2007). Moreover, Schumacher and colleagues (2013) have suggested that sAA may have utility as an indicator of ANS dysregulation in psychiatric disorders. Recently, Ali and Pruessner (2012) highlighted numerous methodological differences in the quantification and analysis of SNS-HPA symmetry in extant research, which may underlie the mixed evidence for its behavioral effects. Therefore, in an effort to standardize assessment of SNS-HPA symmetry, Ali and Pruessner examined the comparative efficacy of the ratio of sAA over cortisol, cortisol over sAA, and either analyte alone for indexing dysregulation across these systems. These authors reported that the sAA/cortisol ratio was more strongly related to subjective indices of depression and chronic stress than its inverse or either analyte alone. In light of evidence for its relative sensitivity for assessing SNS-HPA symmetry and subjective distress (Ali & Pruessner, 2012), investigations of SNS-HPA symmetry and its relation to psychopathology should endeavor to use the sAA/cortisol ratio to assess the degree of association between these systems. Given that anxiety disorders are the most prevalent class of psychiatric morbidity (Kessler et al., 2005) and induce dysregulation across these systems (Schumacher et al., 2013), the dearth of empirical research on SNS-HPA symmetry and pathologic anxiety in adulthood may be an important area of neglect. Moreover, given its high prevalence, relative chronicity, and significant individual and societal cost (Hoffman, Dukes, & Wittchen, 2008; Kessler et al., 2005), it may be particularly important to examine SNS-HPA symmetry in GAD, which has not been previously examined and may further clarify extant research on physiologic functioning in GAD.

The present study compared SNS-HPA symmetry in persons with GAD and healthy controls. In view of some evidence for SNS-HPA asymmetry in adults with anxiety-related pathology (Mason, Giller, Kosten, & Harkness, 1988) and dysregulation across these systems in anxiety disorders (Schumacher et al., 2013), we hypothesized that the presence of GAD would predict greater SNS-HPA asymmetry at both baseline and following a mental arithmetic challenge. Further, in light of evidence for the efficacy of the sAA/cortisol ratio for indexing dissociation between the SNS and the HPA axis (Ali & Pruessner, 2012; Andrews, Ali, & Pruessner, 2013), the present study used the sAA/cortisol ratio to assess SNS-HPA symmetry. Finally, to address limitations presented by use of a ratio variable (Chen, Raine, & Granger, 2015), we used a circumplex plot to further assess relative differences in SNS-HPA symmetry between persons with GAD and healthy controls.

Participants

The present study represents a secondary analysis of previously published data (Fisher & Newman, 2013). A majority of the participants (N = 108) were Caucasian (75%) and female (61%) with a mean age of 19.16 years (SD = 1.53). The Generalized Anxiety Disorder Questionnaire-IV (GADQ-IV; Newman et al., 2002) and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) were used to screen for the presence of GAD. Of the 108 included participants, 71 individuals met criteria for inclusion as GAD participants (65.7%) based on agreement between cutoffs from the GADQ-IV and the MINI, whereas 37 individuals met criteria for inclusion as healthy controls (34.3%). Thirty of the participants that met criteria for GAD also met diagnostic criteria for at least one comorbid Axis I disorder (major depressive disorder, n = 9; panic disorder, n = 3; agoraphobia, n = 11; social phobia, n = 8; posttraumatic stress disorder, n = 2; dysthymia, n = 1; anorexia nervosa, n = 3; obsessive-compulsive disorder, n = 3). Moreover, four included GAD participants were also undergoing psychological treatment.

Procedure

All procedures were authorized by the Institutional Review Board of Pennsylvania State University. Complete details of study procedures can be found in Fisher and Newman (2013). Previously published study procedures include a baseline assessment, experimental induction of worry versus relaxation, and two iterations of the paced auditory serial addition task (PASAT). The current study utilizes endocrinological data drawn from saliva samples collected during the baseline assessment and following the second iteration of the PASAT. The duration of the PASAT was approximately 10 min, including administration and completion. All saliva samples were collected between 11:00 am and 4:00 pm, and each consisted of approximately 200–500 µl of whole unstimulated passive drool. Following Granger, Kivlighan, Fortunato et al. (2007), participants were asked to imagine that they were chewing their favorite food and move their jaws as if they were chewing, allowing saliva to pool under their tongue. Once a pool had developed, they were instructed to gently force the sample through a short plastic straw into a 2-ml cryogenic vial. Participants also rated the extent to which they experienced certain emotions on a 16-item checklist at baseline and after each iteration of the PASAT. Figure 1 depicts a schematic representation of the testing procedure and salivary analyte collection time.

Study Instruments

Emotional responses. Changes in self-reported emotional states were measured using a 16-item emotion checklist (Gross & Levenson, 1993, 1997). This checklist is a self-report inventory consisting of 16 emotion terms (amusement, anger, arousal, confusion, contempt, contentment, disgust, embarrassment, fear, happiness, interest, pain, relief, sadness, surprise, and tension) adapted from Gross and Levenson (1993, 1997). Participants rated the degree to which they were experiencing each emotion using a 9-point Likert-type scale (0 = none, 8 = as much as possible).

GADQ-IV (Newman et al., 2002). The GADQ-IV is a 9-item self-report measure designed to diagnose GAD based on DSM-IV criteria. Using receiver operating characteristic analyses, the
GAD-IV showed 89% specificity and 83% sensitivity when compared to structured interview diagnoses of individuals with GAD, social phobia, panic disorder, and nonanxious controls.

MINI (Sheehan et al., 1998). The MINI is based on diagnostic criteria from the DSM-IV and ICD-10 and has been validated against the Structured Clinical Interview for DSM Disorders (SCID; First, Spitzer, Gibbon, & Williams, 1997). It is designed to be utilized as a short but accurate structured clinical interview for clinical trials and epidemiology studies. Interrater reliability (determined using video recordings) was excellent across all disorders on the MINI (kappa = .89, p < .001) and for the GAD diagnosis specifically (kappa = .95, p < .001).

PASAT. The PASAT is a serial-addition task used to assess working memory, divided attention, and information processing speed, during which a series of random single-digit numbers is presented and participants are required to consecutively add numbers. The PASAT has been shown to reliably induce psychological stress during laboratory inductions (Diehr et al., 2003; Lejuez, Kahler, & Brown, 2003). The duration of the PASAT (including administration and completion) was approximately 10 min in the present study.

Physiological Measures

Cortisol. Saliva samples collected following the diagnostic interview and 20 min after the second iteration of the PASAT, accounting for the kinetic profile of cortisol (Granger, Kivlighan, Fortunato et al., 2007), were assayed for levels of cortisol using a commercially available immunoassay without modification to the manufacturer-recommended protocol (Salimeters, State College, PA). Samples were kept cold (on ice) and then frozen at -20°C following collection. The immunoassay used 25 μl of saliva (for singlet determinations). The test had a lower limit of sensitivity of .007 μg/dl and a range of sensitivity from .007 to 3.0 μg/dl, and average intra- and interassay coefficients of variation of less than 5% and 10%.

Salivary alpha-amylase. SNS activity was measured via levels of sAA, a salivary enzyme involved in the digestion of starch in the oral cavity that has been shown to reflect stress-related changes in SNS arousal (Granger, Kivlighan, El-Sheikh et al., 2007). Saliva samples collected at the end of the diagnostic interview and 5 min after the second iteration of the PASAT, accounting for the kinetic profile of sAA (Granger, Kivlighan, El-Sheikh et al., 2007), were assayed for sAA by kinetic reaction assay (Granger, Blair et al., 2007).

Approach to Modeling SNS-HPA Symmetry

Chen, Raine, and Granger (2015) recently examined the relative utility of modeling interactions between sAA and cortisol via ratios and multiplicative interactions, concluding that each has an appropriate place in biobehavioral research. These authors stated that “the ratio approach is appropriate when it is hypothesized that the two analytes have opposite effects on the same target or one of the analytes cancels out or suppresses the effect of the other” (p. 190). Although the precise nature of the interactions between SNS and HPA axis is still debated (Granger, Kivlighan, El-Sheikh et al., 2007), we contend that a ratio should be given preference when the balance or interaction between these analytes is the dependent variable. This allows the interaction to be represented as a single variable, whereas Chen and colleagues (2015) examined the relative effectiveness of ratios and multiplicative interactions as predictors.

Nevertheless, these authors point out that ratios are limited by their inability to examine the directionality of the interaction between the SNS and the HPA axis. In the present study, we addressed this limitation by representing the relative levels of sAA and cortisol along a circumplex plot. Finally, we tested the relative distribution of sAA and cortisol levels along the circumference of the circumplex in order to further characterize the nature of the interaction (see Results).

Data Preparation and Analysis

Multiple regression analyses were used to compare the sAA/cortisol ratio in GAD and healthy controls at baseline and following a mental arithmetic challenge. All salivary data were log-transformed to correct for positively skewed distributions. Baseline sAA/cortisol was calculated by dividing baseline sAA by baseline cortisol (Ali & Pruessner, 2012). sAA and cortisol levels following the PASAT were calculated by subtracting baseline levels from levels of sAA and cortisol 5 min and 20 min after the PASAT, respectively (see Figure 1). To avoid disagreement in directionality, both variables were displaced at or above zero by adding the absolute value of the minimum value of analyte level following the PASAT. Finally, sAA/cortisol following mental challenge was calculated by dividing the resultant sAA levels by the resultant cortisol levels. Using a subset of emotional responses rated on the 16-item emotion checklist (Gross & Levenson, 1993, 1997), paired t tests were used to examine changes in subjective distress after the PASAT. Paired t tests were also used to examine changes in sAA and cortisol following the PASAT.

To further assess the relative balance between the SNS and the HPA axis arousal, levels of sAA and cortisol were plotted along a circumplex. This allows for assessment of the directionality of SNS-HPA asymmetry, which is obscured by the ratio, using positional information. To accomplish this, salivary measures were
both log- and z-transformed, and the radiant arctangent between the $x$ axis and the vector from origin to $(x, y)$ was derived using the \( \text{atan2} \) function in R. The resultant vector of values (reflecting each sAA/cortisol pair along a circle formed by independent axes of the two variables) was divided into four quadrants, each reflecting the relative balance between the SNS and HPA axis activity in greater detail (see Figure 2). Chi-square goodness of fit tests were then used to compare the relative distribution of GAD and healthy control participants across these quadrants.

**Results**

**Preliminary Group Differences**

Complete details regarding baseline group differences can be found in Fisher and Newman (2013). Results indicated a significant difference in baseline sAA levels between individuals with GAD (\( M = 115.86, SD = 92.42 \)) and healthy controls (\( M = 75.59, SD = 50.09; \beta = .40, SE = .18, t(98) = 2.19, p = .03, d = .30 \)). However, there were no significant group differences in baseline cortisol (\( \beta = -.18, SE = .13, t(98) = -1.39, p = .17, d = -.19 \)), sAA following the PASAT (\( \beta = -.17, SE = .13, t(98) = -1.29, p = .20 \)), or cortisol following the PASAT (\( \beta = .14, SE = .10, t(98) = 1.42, p = .16 \)). Given the presence of psychiatric comorbidities, a regression analysis was conducted to examine differences in sAA/cortisol both at baseline and following mental arithmetic challenge. However, there were no significant group differences in SNS-HPA balance for persons with GAD as a function of comorbidity either at baseline or following the PASAT (\( \beta = .03, SE = .27, t(98) = .15, p = .88 \) and \( \beta = -.24, SE = .20, t(98) = -1.22, p = .23 \), respectively). Therefore, the present study pooled persons with GAD both with and without psychiatric comorbidity into a single group for all analyses. Table 1 displays concentrations of sAA and cortisol by diagnostic group both at baseline and following mental arithmetic challenge.

**Stress Reactivity Following PASAT**

Complete details regarding stress reactivity to the PASAT, demonstrated via decreases in respiratory sinus arrhythmia (RSA), increases in heart rate, and moderated changes in SNS activity indexed by sAA, can be found in Fisher and Newman (2013). Paired \( t \) tests indicated no significant differences in sAA and cortisol following the PASAT. However, a series of paired \( t \) tests indicated significant increases in subjective distress following the PASAT, indexed by increases in anger, confusion, embarrassment, and subjective tension, \( t(106) = 6.82, 4.72, 7.96, \) and \( 5.40, \) respectively, \( p < .001 \). Thus, the PASAT displayed strong convergent validity in eliciting subjective distress.

**Table 1. Means (Standard Deviations) for Salivary Variables by Group at Baseline and Following the Mental Arithmetic Challenge**

<table>
<thead>
<tr>
<th>Variable</th>
<th>GAD (baseline)</th>
<th>Control (baseline)</th>
<th>GAD (post-PASAT)</th>
<th>Control (post-PASAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sAA</td>
<td>115.86 (92.42)</td>
<td>75.59 (50.09)</td>
<td>117.30 (103.40)</td>
<td>87.68 (68.82)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>0.17 (.13)</td>
<td>0.20 (.13)</td>
<td>0.16 (.92)</td>
<td>0.18 (.13)</td>
</tr>
</tbody>
</table>

*Note. GAD = generalized anxiety disorder; sAA = salivary alpha-amylase; cortisol = salivary cortisol; PASAT = paced auditory serial addition task.*
Table 3. Regression of sAA/Cortisol Ratio Following Mental Arithmetic Challenge on GAD Status and Control Parameters

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>SE</th>
<th>t</th>
<th>p</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD</td>
<td>-.39</td>
<td>.18</td>
<td>-2.15</td>
<td>.03</td>
<td>-.42</td>
</tr>
<tr>
<td>BMI</td>
<td>-.00</td>
<td>.02</td>
<td>-0.00</td>
<td>.99</td>
<td>.00</td>
</tr>
<tr>
<td>Sex</td>
<td>-.03</td>
<td>.18</td>
<td>-0.20</td>
<td>.84</td>
<td>-.04</td>
</tr>
<tr>
<td>Smoke</td>
<td>.20</td>
<td>.26</td>
<td>.74</td>
<td>.46</td>
<td>.14</td>
</tr>
<tr>
<td>Sleep</td>
<td>.05</td>
<td>.05</td>
<td>-1.13</td>
<td>.26</td>
<td>-.15</td>
</tr>
<tr>
<td>Exercise</td>
<td>.12</td>
<td>.18</td>
<td>0.68</td>
<td>.68</td>
<td>.13</td>
</tr>
<tr>
<td>Caffeine</td>
<td>.00</td>
<td>.20</td>
<td>0.00</td>
<td>.99</td>
<td>.00</td>
</tr>
<tr>
<td>Caffeine</td>
<td>-.27</td>
<td>.20</td>
<td>-1.40</td>
<td>.16</td>
<td>-.27</td>
</tr>
<tr>
<td>Stress</td>
<td>.37</td>
<td>.20</td>
<td>1.88</td>
<td>.06</td>
<td>.37</td>
</tr>
<tr>
<td>Oral</td>
<td>-.03</td>
<td>.23</td>
<td>-0.14</td>
<td>.89</td>
<td>-.02</td>
</tr>
<tr>
<td>Consume</td>
<td>.11</td>
<td>.18</td>
<td>0.61</td>
<td>.54</td>
<td>.12</td>
</tr>
<tr>
<td>RSA</td>
<td>-.05</td>
<td>.08</td>
<td>-0.59</td>
<td>.56</td>
<td>-.08</td>
</tr>
</tbody>
</table>

Note. d = Cohen’s d (calculated as d = t(2)(98)^1/2); BMI = body mass index; smoke = tobacco use (yes/no); TST = total sleep time for preceding night; exercise = engage in exercise regularly (yes/no); caffeine = ever consume caffeine (yes/no); caffeine = consumed caffeine in the last 6 h (yes/no); stress = experienced any stressful events within last week (yes/no); oral = currently take oral contraception (yes/no); consume = consumed food/liquid in last 2 h (yes/no); RSA = respiratory sinus arrhythmia after mental arithmetic challenge.

Chi-Square Goodness of Fit for Distribution of Quadrants

To further delineate SNS-HPA balance, four chi-square goodness-of-fit tests were conducted to examine the distribution of GAD and healthy control participants across the four quadrants of the circumplex (see Figure 2). Table 4 summarizes the results of these analyses. At baseline, whereas individuals with GAD were roughly evenly distributed across the four circumplex quadrants, χ^2(3, n = 71) = .83, p = .84, there were significantly fewer healthy controls in quadrant II, characterized by high sAA and low cortisol, relative to other quadrants, χ^2(3, n = 57) = 8.30, p = .04. Following the PASAT, individuals with GAD and healthy controls were evenly distributed across the four circumplex quadrants, χ^2(3, n = 71) = 2.18, p = .54 and χ^2(3, n = 36) = 1.56, p = .67, respectively.

Discussion

The present study investigated whether GAD is characterized by SNS-HPA asymmetry. To our knowledge, this is the first study to directly explore the relation between GAD phenomenology and SNS-HPA balance. The present results indicated that, at baseline, persons with GAD exhibited greater sAA/cortisol ratios compared with healthy controls. Further, a complementary analysis revealed that healthy controls were unlikely to exhibit relatively heightened SNS activity coupled with relatively lower HPA axis activity. The results also indicate that persons with GAD exhibited lesser sAA/cortisol ratios relative to healthy controls following a mental arithmetic challenge. These results support the study hypothesis that GAD is characterized by SNS-HPA asymmetry.

Despite theoretical and empirical evidence for SNS-HPA coordination (Andrews et al., 2013), few studies have examined symmetry between these systems and its relation to maladaptive behavior, particularly anxiety-related pathology (Schumacher et al., 2013). Instead, a majority of studies have either opted to monitor only a single system at a time or, when collecting measures of both systems, have neglected to examine proposed imbalance between these systems or its effects. Thus, the present findings complement only a few studies of SNS-HPA asymmetry in children and adolescents with behavior problems (Bauer et al., 2002) and adults with either posttraumatic stress disorder (Mason et al., 1988) or that have experienced early life adversity (Ali & Pruessner, 2012). In addition to these studies, the present results provide additional support for an asymmetry risk model, which predicts that SNS-HPA asymmetry is associated with psychopathology (Bauer et al., 2002). However, mixed results in this domain may imply that there are additional factors that further moderate the relation between SNS-HPA axis symmetry and maladaptive behavior.

Of note, in addition to investigating the presence of SNS-HPA asymmetry in GAD, it is also important to discuss the direction of imbalance across these systems. Careful consideration of the direction of SNS-HPA asymmetry may further clarify extant research on physiologic correlates of GAD. Convergent evidence suggests that GAD is characterized by diminished physiologic flexibility (Hoehn-Saric et al., 1989; Lyonfields, Borkovec, & Thayer, 1995; Thayer, Friedman, & Borkovec, 1996), indexed by peripheral autonomic measures (Hoehn-Saric & McLeod, 1988). With respect to sympathetic functioning, Fisher and Newman (2013) recently demonstrated that higher baseline SNS activity, indexed by sAA, predicted significant decreases in SNS arousal for persons with GAD following a mental arithmetic challenge, whereas greater baseline SNS arousal predicted significant increases in SNS arousal in healthy controls. These findings are consistent with Fisher, Granger, and Newman (2010), wherein greater baseline SNS arousal predicted lesser change in SNS response. The authors...
propose that these results reflect a suppression of SNS reactivity in GAD.

The present study further extends these results. As noted above, cortisol plays permissive and suppressive roles in adaptive physiology functioning (Sapolsky et al., 2000). These effects occur in response to both mild and more drastic shifts in environmental demands, thereby allowing for flexible physiologic response. Importantly, Sapolsky and colleagues (2000) state that the permissive—or enhancing—effects of cortisol depend upon basal levels, whereas suppressive—or constraining—effects depend upon changes in cortisol level. With respect to sympathetic response to challenge, it follows that relatively less cortisol at baseline would predict lessened initiation of SNS arousal in response to an environmental challenge. Further, greater relative level of cortisol following a challenge, relative to stress-induced SNS arousal, would reflect enhanced suppression of SNS reactivity. The present study reported that GAD is characterized by less cortisol relative to sAA at baseline and greater cortisol relative to sAA following a mental arithmetic challenge. This implies that suppression of SNS reactivity in GAD—manifested in decreases in sAA after a mental arithmetic challenge (Fisher & Newman, 2013)—is partially mediated by decreased initiation of SNS arousal and enhanced SNS suppression by cortisol.

There are several important limitations of the current study. First, recruitment from a large undergraduate pool limited the ethnic diversity and age range of the study sample, thereby limiting generalizability. Further, GAD status required agreement between a validated diagnostic inventory and structured clinical interview (Newman et al., 2002; Sheehan et al., 1998). Although an independent diagnosis of GAD using the structured clinical interview required the presence of clinically significant impairment or distress, which strengthens the relevance of these findings to clinically severe cases of GAD, participants in this study were not treatment seeking. Therefore, these findings should be replicated with representative treatment-seeking samples drawn from community populations. Second, although evidence suggests sAA concentrations vary independently of menstrual phase (Rohleder & Nater, 2009), menstrual phase has been shown to affect cortisol levels (Helmhammer et al., 2009). Thus, future studies utilizing female participants should also account for menstrual cycle phase and its effects on HPA axis activity. Third, there is some debate regarding the validity of sAA as a surrogate marker of the SNS (Nater & Rohleder, 2009). For instance, Bosch, Veerman, de Geus, and Proctor (2011) recently provided evidence that parasympathetic efferents also play a significant role in sAA release, thereby challenging the interpretation of sAA as a purely sympathetic index. Although the present study accounted for concurrent parasympathetic activity, future studies should seek to replicate these findings using measures that reflect underlying SNS activity with a greater degree of specificity.

Fourth, although there is evidence that mental arithmetic challenge elicits increases in SNS activity and decreases in parasympathetic activity (Maundner, Lancee, Nolan, Hunter, & Tannenbaum, 2006; Noll et al., 1996; Wilkinson et al., 1998), the present results only imply mild perturbations of underlying physiologic systems expected to occur under ecologically valid situations (i.e., mild to moderate cognitive challenge). Future studies should also endeavor to replicate these findings using alternative stress paradigms to elicit more significant perturbations in SNS and HPA axis activity. Lastly, in the present study, assessment of SNS-HPA asymmetry following a mental arithmetic challenge was taken from saliva samples collected with a time delay, thereby accounting for the kinetic profiles of the target analytes (Granger, Kivlighan, El-Sheikh et al., 2007; Granger, Kivlighan, Fortunato et al., 2007). However, given that sAA and cortisol concentrations are expected to peak at specific times following stressor onset, the present sampling method of collecting saliva samples at a set time following conclusion of the mental arithmetic task may challenge the validity of these results. Thus, although we contend that the present design provided an acceptable approximation of the expected response profile of each analyte, future studies should employ more intensive repeated measures designs to further characterize the asymmetric response dynamics of these systems in GAD.

Despite these limitations, the present study represents an important exploration and extension of research on the physiologic correlates of GAD. Specifically, whereas extant research has examined either ANS or HPA axis activity in GAD, this study used a ratio approach to examine the degree of symmetry between these systems that interact and synchronize to maintain adaptive physiologic functioning in persons with GAD (Ali & Pruessner, 2012; Andrews et al., 2013; Schumacher et al., 2013). This study also provides additional support for the utility of the sAA over cortisol ratio to index dysregulation across the stress system (Ali & Pruessner, 2012). Finally, despite its pathologic role in GAD, it is important to note that worry is a dimensional process that moves along a continuum of adaptive to clinically impairing (Barlow, 2004). Therefore, future studies should also evaluate whether the process of worry specifically promotes dysregulation across the stress system in both persons with GAD and nonclinical populations using the sAA over cortisol ratio.

References


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