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Psychophysiological Correlates of Generalized Anxiety Disorder with or without Comorbid Depression

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Abstract

It remains uncertain whether generalized anxiety disorder (GAD) and major depressive disorder (MDD) represent two separate diagnostic entities. The goal of this study was to examine whether comorbid MDD distinguishes individuals with GAD on a psychophysiological level during an experimentally-induced worrying procedure. Participants included 39 individuals with GAD, 14 of whom met criteria for MDD. During the experimental procedure, participants were asked to worry or relax after an initial baseline phase while measuring their heart rate, high frequency heart rate variability (HF-HRV), skin conductance level, and subjective level of anxiety. The two groups did not differ in their subjective anxiety, heart rate response, and skin conductance levels. However, participants with comorbid MDD had greater HF-HRV values throughout the experiment than did those without MDD. At baseline, HF-HRV was significantly correlated with a self-report measure of depression. These results suggest that individuals with comorbid GAD and MDD can be distinguished based on HF-HRV from individuals with GAD but without MDD. These results support the distinction between GAD and MDD.

Keywords

Generalized Anxiety Disorder; Depression; Autonomic Arousal; Heart Rate; Heart Rate Variability; Skin Conductance Level; Worrying

Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are highly comorbid, as suggested by a number of epidemiological studies (Breslau, Schultz, & Peterson, 1995; Kessler, Nelson, McGonagle, Liu, Swartz, & Blazer, 1996; Kessler, Brandenburg, Lane, Roy-Byrne, Stang, Stein, & Wittchen, 2005). Approximately two thirds of patients with a lifetime diagnosis of GAD retrospectively report MDD, but only approximately one fifth of patients with a lifetime diagnosis of MDD retrospectively report GAD (Kessler, DuPont, Berglund, & Wittchen, 1995), suggesting that generalized anxiety tends to precede depression and eventually develops into depression. However, a recent prospective longitudinal cohort study from New Zealand challenged this notion, because the reverse temporal relationship occurs almost as often (Moffitt, Harrington, Caspi, & Kim-Cohen, 2007). The authors further concluded that the relationship between GAD and MDD is strong, suggesting that the disorders could be classified in one category of distress disorders.

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GAD was first defined in DSM-III and was characterized by fluctuating levels of uncontrollable worry associated with fatigue, insomnia, muscle tension, poor concentration, and irritability, which are also typical symptoms of depression. In DSM-III, individuals could not receive a diagnosis of an anxiety disorder if the anxiety symptoms occurred during episodes of depression. This hierarchy rule was eliminated in the DSM-III-R for all anxiety disorders except GAD. According to DSM-IV, GAD can only be assigned in individuals with MDD if the GAD symptoms also occur outside a depressive episode. Thus, DSM-IV precludes the diagnosis of GAD for individuals who experience symptoms of GAD only during depressive episodes. These nosological rules reflect the uncertainty as to whether GAD and MDD represent two separate diagnostic entities and whether the comorbidity between the two disorders identifies a unique group of individuals (Mineka, Watson, & Clark, 1999; Zahn-Waxler, Klimes-Dougan, Slaterry, 2000). The empirical evidence to inform the upcoming DSM-V criteria on the overlap between GAD and MDD are primarily based on interview and questionnaire data from epidemiological surveys (see Hettema, 2008, for a review).

Psychophysiological experiments are another valuable source of data to clarify the relationship between GAD and MDD. Among the autonomic measures, cardiac vagal tone has gained an increasing amount of attention (Porges, 2007). Low cardiac vagal tone has been associated with a number of psychopathological states, including depression (Rottenberg, 2007), anxiety (Friedman, 2007), and the cognitive processes that have been associated with depression and anxiety, namely rumination (Nolen-Hoeksema & Davis, 1999) and worrying (Borkovec, Ray, & Stöber, 1998).

Worrying has been associated with reduced autonomic flexibility as a result of low cardiac vagal tone (Borkovec & Hu, 1990; Hoehn-Saric & McLeod, 2000; Hofmann, Moscovitch, Litz, Kim, Davis, & Pizzagalli, 2005; Lyonfields, Borkovec, & Thayer, 1995; Thayer, Friedman, & Borkovec, 1996) and higher skin conductance levels (Fowles, 1980; Hofmann et al., 2005; Roth et al., 2008). Other studies, however, were unable to demonstrate the effect of worrying on cardiac activity (Davis, Montgomery, & Wilson, 2002; Hazlett-Stevens & Borkovec, 2001); for a review, see Friedman (2007). Similarly, the review of the depression literature on cardiac vagal tone has been mixed (Rottenberg, 2007).

Both rumination and worrying are repetitive thought styles that are closely correlated (Watkins, 2004). However, it has been suggested that there are important differences in the functions of these cognitive processes for the maintenance of the disorders. Specifically, rumination refers to the tendency to focus on the causes and consequences of past problems without moving into active problem solving (Nolen-Hoeksema, 2000). In contrast, worrying is an anticipatory process attempting to prevent or minimize future problems and may act as a cognitive avoidance strategy to reduce negative emotions associated with intrusive catastrophic images (Borkovec et al., 1998). A number of recent empirical studies support this distinction (Fresco, Frankel, Mennin, Turk, & Heimberg, 2002; Segerstrom, Stanton, Alden, & Shortridge, 2003). It is possible that depression, a frequently comorbid condition, moderates the effects of worrying on psychophysiological arousal, because worrying may have a different function in GAD when MDD is a comorbid diagnosis. This could explain the inconsistent findings reported in the literature with regard to the psychophysiological effects of worrying.

In sum, the relationship between GAD and MDD remains a controversial issue with important implications for the DSM-V. Moreover, experimental studies on the psychophysiological correlates of worrying, the cognitive process closely associated with GAD, have not systematically accounted for the possible influence of comorbid MDD. Furthermore, the literature on the psychophysiology of worrying and GAD has been very inconsistent, and it is possible that the comorbid diagnosis of MDD may in part account for this inconsistency. Therefore, the goal of the present study was to examine whether the comorbid diagnosis of

MDD in patients with GAD is associated with different psychophysiological correlates during worrying compared to GAD patients without MDD. Consistent with the literature, we examined the differences between these diagnostic subgroups in HF-HRV (e.g., Thayer et al., 1996) and electrodermal activity (e.g., Fowles, 1980).

Method

Participants

The sample consisted of 39 patients with GAD who presented for assessment at the Center for Anxiety and Related Disorders at Boston University. Women constituted the larger portion of the sample (71.79%), with an average age of 28 ($SD = 9.92$, range = 19 to 65). Participants were largely Caucasian (89.74%), with smaller numbers of individuals identifying as Asian (2.56%), Hispanic (2.56%), and African-American (2.56%).

The two groups (without vs. with depression) did not differ in the type of medication they received, including selective serotonin reuptake inhibitors (40.0% vs. 35.71%), $\chi^2(1) = .07$, $p = 0.99$; tricyclic antidepressants (8.00% vs. 0.00%), $\chi^2(1) = 1.18$, $p = .53$; benzodiazepines (24.00% vs. 0.00%), $\chi^2(1) = 3.97$, $p = .07$; contraception (20.00% vs. 28.57%), $\chi^2(1) = .37$, $p = .70$; stimulants (4.00% vs. 7.00%), $\chi^2(1) = .18$, $p = .99$, and analgesics (0.00% vs. 14.29%), $\chi^2(1) = .94$, $p = .99$. Finally, the two groups did not differ in the average number of different medications they took, $t(37) = 0.14$, $p = .99$ (all Fisher's exact tests).

Diagnostic Assessment

Diagnoses were established with the Anxiety Disorders Interview Schedule for DSM-IV: Lifetime version (ADIS-IV-L; Di Nardo, Brown, & Barlow, 1994). The ADIS-IV-L is a semi-structured interview that assesses DSM-IV anxiety, mood, somatoform, and substance use disorders, and screens for the presence of other conditions (e.g., psychotic disorders). When administering the ADIS-IV-L, interviewers assign a 0–8 clinical severity rating (CSR) that reflects the degree of distress and impairment associated with the disorder (0 = “none” to 8 = “very severely disturbing/disabling”). A CSR of 4 or higher reflects presence of a condition that is clinically significant in terms of distress or impairment. Only participants who met DSM-IV criteria for GAD as their principal (most distressing/interfering diagnosis) were included in the study.

Participants in this study did not undergo a second diagnostic assessment. However, the clinicians at our center underwent a rigorous diagnostic training procedure, and all diagnostic assessments were discussed in weekly meetings led by the co-developer of the ADIS-IV, Dr. Timothy Brown. A previous reliability study with clinicians who underwent the same training procedure resulted in diagnostic data with satisfactory reliability (Brown, Di Nardo, Lehman, & Campbell, 2001). This study indicated good to excellent interrater agreement for the majority of anxiety and mood disorders. Although GAD had the lowest interrater agreement among the anxiety disorders (Kappa = .67), the level of agreement is still more than satisfactory. When GAD was diagnosed as an additional diagnosis the Kappa was .59, which is still acceptable. According to general guidelines (Landis & Koch, 1977) a Kappa coefficient of 0.67 is considered “good agreement” (Kappa range: 0.61–0.90), and a Kappa of 0.59 is considered “moderate agreement” (Kappa range: 0.41–0.60).

Study Groups

Out of 39 clinical participants with GAD, 14 met criteria for an additional current diagnosis of major depressive disorder (MDD), whereas 25 did not. These two groups did not differ on comorbidity with any other anxiety disorder, $\chi^2(1) = 3.56$, $p = .08$. Furthermore, the groups

did not differ on the distress ($p > .4$), interference ($p > .4$), and symptom severity ratings ($p > .5$) of GAD or on any demographic variables (all p 's $> .3$).

Questionnaires

Upon arrival at the laboratory, participants were briefed about the procedures and written consent was obtained for the study. After patients had signed the informed consent form (approved by the Institutional Review Board of Boston University), they were asked to complete the following self-report instruments:

Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990) is a 16-item self-report questionnaire measuring the general tendency toward excessive worrying, without reference to specific content. It shows very good reliability (Molina & Borkovec, 1994), convergent and discriminant validity (cf. Brown, Antony, and Barlow, 1992), and treatment sensitivity (Borkovec & Costello, 1993). The scale was administered to measure the degree of worrying, which is a defining clinical feature of GAD.

Beck Depression Inventory - Second Edition (BDI-II, Beck, Steer, & Brown, 1996) is a 21-item self-report questionnaire assessing the severity of symptoms of depression over the past two weeks. This frequently-used instrument shows high internal consistency ($\alpha = 0.93$ and 0.92 in samples of college students and outpatients respectively, Beck, Steer, Ball, & Ranieri, 1996) and has been shown to be a valid indicator of depression with good diagnostic discrimination (Dozois, Dobson, & Ahnberg, 1998).

Experimental Procedure

As part of the laboratory experiment, which lasted approximately 30 minutes, patients' autonomic indicators (heart rate, respiratory sinus arrhythmia, and skin conductance level) were measured in response to the worry and relaxation instructions. After the electrodes were attached, patients were seated in a comfortable chair in the testing room while the experimenter was in the adjacent room, communicating with the patient over an intercom. The two rooms were separated by a 1-way mirror. After providing general instructions on how to use a simple intercom device, the participants were left alone in the room, with the door closed, during the rest of the experiment. The experimental sessions consisted of a number of tasks that have been used in previous studies, including some of our own (e.g., Hofmann et al., 2005).

The experiment began with an initial 5-minute baseline phase during which participants were instructed to close their eyes and to breathe normally. This was followed by a 5-minute worrying phase or a 5-minute relaxation phase. The task order for the worrying and relaxation phases was randomly determined. A comparison between the study groups on the task order assignment suggested that the random assignment was successful, $\chi^2(1) = .43$, $p > .6$. The worrying instructions asked participants to worry about their most worrisome topic. This topic was identified during the diagnostic interview. Examples included money, health, world affairs, relationships, etc. Specifically, participants received the following instructions:

During the next 5 minutes, we'd like you to worry about the topic you tend to worry most often and most intensely about. We know, this may not be the most pleasant thing to do, but it is a very important part of this study to better understand the effects of worrying. Please, close your eyes, and try to worry for the complete 5 minutes. If you realize your attention starts wandering off, try to refocus on the topic.

For the 5-minute relaxation phase, participants were instructed to close their eyes and *relax as much as possible*. The experiment ended with a 2-minute recovery phase during which participants were asked to sit quietly with their eyes closed and to breathe normally.

Subjective Ratings

After each experimental task, participants were asked to rate their (1) average level of anxiety and (2) worry intensity during this task on a scale from 0 = not at all, to 10 = extremely.

Psychophysiological Measurements

All measures were recorded with equipment by James Long Company (Caroga Lake, New York) and with the data-acquisition program Snap-Master™ for Windows. The system allows for continuous collection of the recordings. The physiological measures were digitized at 512 samples per second with a 31-channel A/D converter operating at a resolution of 12 bits and having an input range of −2.5 volts to +2.5 volts. Autonomic indicators included heart rate, HF-HRV and electrodermal activity (skin conductance level). All psychophysiological channels were amplified by individual SA Instrumentation Bioamplifiers. The amplification rates and high-pass filter (HPF) and low-pass filter (LPF) settings were as follows: electrocardiogram (gain = 500, HPF = 0.1 Hz, LPF = 1000 Hz), and skin conductance level (gain = 0.1 volt per microsiemens, HPF = none/DC, LPF = 10 Hz). HF-HRV and electrodermal activity, as indexed by skin conductance level (SCL), were the two main dependent measures. These two parameters were theoretically identified as the primary variables because they are indices of the two branches of the autonomic nervous system.

During the collection of the data, the onset and termination of experimental phases were defined using an event marker, which was engaged manually by the experimenter at the appropriate times. Average values of the psychophysiological variables were computed for each period of interest. In order to obtain reliable results of the spectral analysis for HRV-HF, we collapsed the recording across each of the experimental tasks.

Heart Rate—The plus and minus channel of the grounded electrocardiogram was recorded through disposable CardioSens/K Resting ECG Electrodes (Part No. 047866) that were attached to either side of the participants' lowest ribs. Target skin areas were cleaned with alcohol wipes and allowed to dry. EKG R-peaks and artifact periods were automatically detected with the IBI Analysis System (James Long Company; Caroga Lake, NY). Subsequent visual control by the experimenter included inspection of the raw EKG, scoring of R-waves that were missed by the automated detection, and removal of R-wave identification marks that were incorrectly specified (e.g., a movement artifact that the computer coded as an R-wave). Finally, less than 1% of R-peaks (e.g., ectopic beats) were estimated using cubic spline interpolation of adjacent points with a custom MATLAB (Mathworks, Inc., Natick, MA) program. Heart rate was computed as number of R-waves per minute. The Kolmogorov-Smirnov Z-test showed that heart rate was normally distributed during all study tasks (all Z 's < .99; p 's > .28). Therefore, no statistical transformation was necessary.

High Frequency Heart Rate Variability—Five-minute segments of instantaneous R–R intervals matching the experimental conditions (baseline, relaxation, worry) were imported to HF-HRV Analysis Software 1.1. SP1 (Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland, <http://bsamig.uku.fi/>), prorated to equidistant time series using cubic interpolation (8Hz), and subjected to a fast Fourier transform using Welch's algorithm (program settings: points in frequency domain: 1024, window size: 512, overlap: 50%). HF-HRV was then derived as a measure of parasympathetic cardiac control by integrating over the high frequency (HF) spectral component of R–R intervals at 0.15–0.40 Hz (in ms^2 ; see Camm et al., 1996). This high-frequency peak is thought to reflect the magnitude of respiratory sinus arrhythmia (RSA) without requiring the assessment of respiratory rate (e.g., Akselrod Gordon, Ubel, Shannon, Berger, & Cohen, 1981; Denver, Reed, & Porges, 2007; Porges & Bohrer, 1990). The Kolmogorov-Smirnov Z-test showed that HF-HRV was not

normally distributed during any of the study tasks (all Z 's > 1.48 ; p 's $< .03$). Therefore, we performed a log10 transformation of the recorded values.

Electrodermal Activity—Skin conductance level was measured using two Ag-AgCl electrodes filled with electroconductive gel that were attached to the palmar surface of the middle phalanges of the third and fourth fingers of the non-dominant (left) hand. Participants washed their hands with water before the electrodes were attached. Skin conductance level was averaged over the experimental conditions (baseline, relaxation, worry) and is reported here in micro Siemens. The Kolmogorov-Smirnov Z -test showed that skin conductance level was normally distributed during all study tasks (all Z 's < 1.00 ; p 's $> .26$). Therefore, no statistical transformation was necessary.

Results

Worry Ratings (Manipulation Check)

To examine whether the worry task had the intended effect, we conducted a 2 (Group: GAD participants with vs. without depression) by 4 (Time: baseline, relaxation, worrying, recovery) repeated measures ANOVA with the worry intensity ratings as the dependent variable. The results showed the expected significant Time effect, $F(3, 33) = 3.71$, $p < .0001$, $\eta_p^2 = .67$, but no Group ($p > .4$) or Group by Time interaction effect ($p > .3$). During the worry task, the worry ratings were similarly high ($p > .5$) in the GAD without MDD group and the GAD with MDD group. The ratings during the worry task were higher than the worry ratings during any of the other tasks in both groups (all p 's $< .0001$). The means and standard deviations of the subjective ratings and all psychophysiological measures are presented in Table 1.

Questionnaires

As expected, GAD participants with MDD showed higher BDI scores ($M: 27.93$, $SD: 10.17$) than did GAD participants without MDD ($M: 17.63$, $SD: 8.67$), $t(36) = 3.32$, $p < .002$. However, the two groups did not differ on PSWQ scores ($p > .6$).

Subjective Anxiety Ratings

To examine changes in participants' subjective anxiety response, we conducted a 2 (Group: GAD participants with vs. without depression) by 4 (Time: baseline, relaxation, worrying, recovery) repeated measures ANOVA with the subjective anxiety ratings as the dependent variable. The results showed a significant Time effect, $F(3, 33) = 3.71$, $p = .021$, $\eta_p^2 = .25$, but no Group ($p > .4$) or Group by Time interaction effect ($p > .2$). The Time effect was associated with a significant quadratic trend, $F(1, 35) = 10.13$, $p = .003$, $\eta_p^2 = .23$, indicating that participants reported greater anxiety during the worrying condition ($M: 5.16$, $SD: 2.64$) and the relaxation condition ($M: 5.27$, $SD: 2.55$) than during the baseline ($M: 4.65$, $SD: 2.47$) and recovery phases ($M: 4.22$, $SD: 2.24$).

Heart Rate

In order to examine the difference between GAD participants with and without depression in general autonomic arousal, we compared the two groups on their heart rate response during the experiment.¹ A 2 (Group) by 4 (Time) repeated measures ANOVA showed no significant Group effect, $F(1, 35) = .89$, $p > .3$, $\eta_p^2 < .03$, or Group by Time interaction effect $F(2.1, 73.8) = 2.74$, $p > .5$, $\eta_p^2 < .02$. The Time effect also did not reach the level of statistical significance, $F(2.1, 73.8) = 2.74$, $p = .06$, $\eta_p^2 = .07$ (with Greenhouse-Geisser correction because of sphericity violation).

High Frequency Heart Rate Variability

We conducted a 2 (Group) by 4 (Time) repeated measures ANOVA with the log10 transformed HF-HRV data as the dependent variable. The results revealed a significant Group effect, $F(1, 36) = 4.41, p = .04, \eta_p^2 = .11$. The Time and Group by Time interaction effects were not significant ($p > .3$). Participants with depression had higher HF-HRV ($M: 2.69, SE: 0.10$) than those without depression ($M: 2.36, SE: 0.13$).

Skin Conductance Level

A 2 (Group) by 4 (Time) repeated measures ANOVA showed a significant Time effect, $F(2.41, 86.79) = 9.34, p < .0001, \eta_p^2 = .21$ (with Greenhouse-Geisser correction because of sphericity violation). The Group and Time by Group interaction effects were not statistically significant (all p 's $> .15, \eta_p^2 < .05$). The Time effect was associated with a significant linear trend in SCL, $F(1, 36) = 15.79, p < .0001, \eta_p^2 = .31$ showing increasing levels of SCL from baseline ($M: 7.20, SE: .66$), to relaxation ($M: 7.84, SE: .77$), and worrying ($M: 8.01, SE: .80$), to recovery ($M: 8.26, SE: .83$).

Covariation Between Autonomic Arousal, Depression and Worrying

To further examine the relationship between depression, worrying, SCL, and HF-HRV, we conducted product-moment correlations between the BDI scores, the PSWQ scores, and the two autonomic measures (HF-HRV and SCL) across all participants during the baseline phase of the experiment. We limited this analysis to the baseline phase because the experimental instructions restrict the variance between participants.

The results showed no significant correlation between SCL and the BDI scores, $r(n = 37) = .23, p = .17$, and also no significant correlation between SCL and the PSWQ scores, $r(n = 37) = .09, p = .59$. However, HF-HRV was significantly correlated with the BDI, $r(n = 37) = .35, p = .032$, but no significant covariation was observed between HF-HRV and the PSWQ, $r(n = 37) = .09, p > .6$.

Discussion

The underlying pathological cognitive process of GAD is worrying, which has been associated with reduced autonomic flexibility as a result of low cardiac vagal tone (Borkovec & Hu, 1990; Hoehn-Saric & McLeod, 2000; Hofmann et al., 2005; Lyonfields, Borkovec, & Thayer, 1995; Thayer, Friedman, & Borkovec, 1996). For example, Thayer and colleagues (1996) showed that, relative to baseline and relaxation conditions, experimentally induced worrying was associated with higher heart rate but lower cardiac vagal tone. Other studies, however, were unable to demonstrate the psychophysiological effects of worrying (Davis, Montgomery, & Wilson, 2002; Hazlett-Stevens & Borkovec, 2001). Furthermore, some authors have argued that electrodermal activity is a better psychophysiological correlate of worrying than cardiac activity (e.g., Fowles, 1980).

It is possible that the inconsistency in the literature might have been due to the heterogeneity of the GAD diagnosis, and specifically to the comorbidity with depression. No study to date

¹It is sometimes assumed that the psychophysiological system responds less when it is operating at a higher output level than when it is operating at a lower level. Therefore, higher baseline levels of a physiological variable should result in a limited increase, whereas lower levels might result in a limited decrease in this variable. This has been termed the "law of initial values" (Wilder, 1958) and the "principle of initial values" (Stern, Ray, Quigley, 2001). However, the empirical data do not support the basic premise of this law/principle (e.g., Myrtek and Foerster, 1986). For example, the correlation between baseline HF-HRV and the HF-HRV change score from baseline to the worry period was $r = 0.16$ in the present study. Therefore, it has been suggested that it is inappropriate to use covariate analyses in order to "correct for" difference between groups at baseline (Jennings & Gianaros 2001; Miller & Chapman, 2001). For these reasons, we decided not to include basal level as covariates in the analyses.

has specifically examined the role of depression in the psychophysiological response to worrying among individuals with GAD. In order to fill this gap in the literature and to examine whether the comorbid diagnosis of MDD can distinguish individuals with GAD on an autonomic level, 14 individuals with GAD and MDD were compared with 25 participants with GAD but no current diagnosis of MDD.

The two groups did not differ in the clinical severity of GAD, degree of worrying, or any demographic variables. During the baseline phase and an experimental procedure to induce worrying or relaxation, the two groups did not differ in their subjective anxiety, heart rate response, or skin conductance level, but the experimental procedure led to significant changes from baseline in subjective anxiety and skin conductance level. The worry instructions had the intended effect as indicated by worry ratings. Most importantly, participants with comorbid MDD had greater HF-HRV values throughout the experiment than those without MDD.

Interestingly, participants reported relatively high subjective anxiety during the relaxation task. Although this seems surprising, it is actually consistent with earlier studies demonstrating relaxation-induced anxiety (Heide & Borkovec, 1984a, b) and also more recent studies on the effects of relaxation strategies on anxiety (Conrad, Isaac, & Roth, 2008a, b). For example, Conrad, Isaac and Roth (2008a) observed that instructions to sit quietly (a task that is comparable to the baseline assessment in the current task) and instructions to relax did not differ on most psychological and physiological measures, indicating that intention to relax did not affect speed of relaxation in GAD patients. This is at odds with results of studies comparing relaxation and worry instructions in nonclinical populations (e.g., Hofmann et al., 2005), suggesting that a clinical population of GAD patients experiences the relaxation instructions under experimental conditions as a stressful task. In a later experiment, Conrad, Isaac, and Roth (2008b) further found that applied relaxation led to greater symptom improvement than a waitlist control condition. However, the authors found little evidence that participants in the applied relaxation group learned to relax in therapy or that a reduction in anxiety was associated with a decrease in physiological activation. However, this does not necessarily imply that relaxation strategies are generally ineffective or contraindicated for GAD. A number of studies suggest that relaxation trainings contain active mechanisms of change (e.g., Borkovec & Costello, 1993; Borkovec, Newman, Pincus, & Lytle, 2002).

Of all the physiological indicators, only HF-HRV, a measure of cardiac vagal tone, distinguished the two study groups; GAD patients with MDD showed *greater* HF-HRV than did patients without MDD. A correlation between the BDI scores and HF-HRV values during baseline was statistically significant and at a moderate range. The reason for this association is not obvious. GAD and MDD are highly overlapping disorders. It is possible that the cognitive processes associated with the two disorders have differential psychophysiological correlates. Worrying has been primarily examined in relation to GAD (e.g., Borkovec, Ray, & Stöber, 1998), whereas rumination has been most closely studied in the context of MDD (Nolen-Hoeksema & Davis, 1999). Rumination refers to the tendency to focus on the causes and consequences of problems without moving into active problem solving (e.g., Nolen-Hoeksema, 2000), whereas worrying may be an attempt to prevent or minimize future problems and may, therefore, act as a cognitive avoidance strategy to reduce negative emotions associated with intrusive catastrophic images (Borkovec et al., 1998). Although phenomenologically related (Watkins, 2004), worrying and rumination may serve different functions and have different psychophysiological correlates. More specifically, our results suggest that worrying may only be associated with autonomic inflexibility in the absence of MDD, whereas the function of worrying changes if MDD is present as a comorbid diagnosis. This result is somewhat surprising because MDD is similarly associated with autonomic inflexibility (Gorman & Sloan, 2000). Because this effect is already apparent at baseline, HF-HRV might serve as a valuable diagnostic marker of MDD as a comorbid diagnosis of individuals with GAD. It has been

suggested that the physiological suppression associated with worrying is linked to the verbal-linguistic processes that occur during worrying (Borkovec, Alcaine, & Behar, 2003), whereas depressive rumination may be associated with more imagery than verbal processes (McLaughlin, Sibrava, & Borkovec, 2007). Therefore, it is possible that our results reflect differences in the verbal and imagery processes that are associated with worrying and rumination, which might explain why depression is associated with increases in vagal tone among individuals with GAD. Future studies should examine differences between GAD patients with and without MDD in other psychophysiological measures, including startle and brain activation (Lang & McTeague, 2009). It may also be interesting to examine whether the presence of depression has a positive effect on fear activation necessary for extinction learning.

A number of limitations should be considered when interpreting these findings. First, the sample size is relatively small, and we did not include a group of participants with MDD but without GAD. Second, although the groups did not differ on any relevant sociodemographic or clinical characteristics, the quasi-experimental nature of the study cannot rule out the influence of third variables. Third, the relatively high values of SCL during recovery are unusual and probably due to the shorter (2-minute) task length as compared to the other (5 minute) tasks. Furthermore, due to the randomization of the worry and relaxation tasks, the recovery has different meanings, especially since it was so short. Fourth, the use of HF-HRV as a measure of vagal tone is not without controversy. A number of factors can contribute to any possible group differences in this variable, including demographic and anthropometric factors or differences in residual physical activity in the laboratory situation (Grossman & Taylor, 2007). Given the residual inspiratory vagal activity that is not highly correlated with HF-HRV, it is not possible to accurately estimate individual differences in cardiac vagal activity from common high-frequency HF-HRV measures (Grossman & Kollai, 1993; Kollai & Mizsei, 1990; Ritz & Dahme, 2006; Ritz, 2009). For example, Kollai and Mizsei (1990) reported that during normal breathing the correlation across participants between respiratory sinus arrhythmia and vagal control was only moderately strong, and this relationship was not affected by beta-adrenergic blockade. This association is improved when considering respiratory parameters (Kollai & Mizsei, 1990) and heart rate (Grossman & Kollai, 1993). Fifth, it has been noted that respiration greatly influences measures of vagal tone between and within individuals. Studies have shown that both tidal volume and respiration rate have profound effects on measures of vagal tone (Grossman et al., 1991; Ritz & Dahme, 2006). In the within-individual case, these effects can mask or produce “spurious” task effects on cardiac vagal activity when tasks also affect respiration rate and/or tidal volume. For example, a hypothesized increase in vagal tone during relaxation could be produced by an increase in tidal volume and/or a decrease in respiration rate, which is a typical breathing pattern in relaxation. Without controlling for respiratory parameters it is not possible to clearly interpret HF-HRV measures in terms of vagal activity changes. For example, it could be that the respiratory effects on HF-HRV were cancelled out by vagal withdrawal under this condition in patients, if the relaxation instruction was perceived as anxiety-inducing in the laboratory situation. Some authors, however, have questioned the assumption that respiration needs to be manipulated or monitored to generate an accurate measure of cardiac vagal control (Akselrod et al., 1981; Denver, Reed, & Porges, 2007; Porges, 2007; Porges & Bohrer, 1990). Given these limitations, it is important to use caution when interpreting the data and especially when using a single measure, such as HF-HRV, as an indicator of vagal tone. Moreover, there was no healthy control group to allow examination of whether HF-HRV values were unusually low in GAD patients without MDD or unusually high in those with MDD. Such a comparison would have strengthened the interpretability of the findings. Finally, it would have been desirable to conduct a second diagnostic interview by an independent assessor in order to determine the reliability of the clinical assessment procedure and to know the history of any past diagnoses, including depression.

Despite these limitations, the results of this study suggest that individuals with comorbid GAD and MDD can be distinguished based on HF-HRV from individuals with GAD but without MDD even at a baseline phase. These results support the distinction between the two disorders.

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Table 1

Comparison Between Study Groups in Their Psychophysiological Response to the Experimental Tasks.

		GAD without MDD	GAD with MDD
Anxiety (ratings 0–10)	Baseline	4.42 (2.47)	5.08 (2.53)
	Relaxation	5.54 (2.43)	4.77 (2.77)
	Worrying	4.71 (2.76)	6.00 (2.27)
	Recovery	3.96 (2.22)	4.69 (2.29)
Worry (ratings 0–10)	Baseline	4.25 (2.23)	4.77 (2.55)
	Relaxation	3.83 (2.26)	3.69 (2.29)
	Worrying	6.92 (1.56)	7.23 (1.64)
	Recovery	3.83 (2.18)	4.77 (1.79)
Heart Rate (beats per minute)	Baseline	74.66 (9.17)	71.92 (12.14)
	Relaxation	74.67 (10.34)	70.67 (11.99)
	Worrying	75.42 (9.73)	72.47 (13.02)
	Recovery	74.12 (10.87)	69.83 (12.10)
HF-HRV (ms ²)	Baseline	2.45 (0.42)	2.70 (0.64)
	Relaxation	2.40 (0.42)	2.69 (0.65)
	Worrying	2.29 (0.41)	2.62 (0.77)
	Recovery	2.31 (0.51)	2.76 (0.69)
SCL (micro Siemens)	Baseline	6.54 (3.35)	7.87 (4.71)
	Relaxation	6.85 (3.57)	8.82 (5.93)
	Worrying	7.08 (3.79)	8.94 (6.10)
	Recovery	7.12 (3.91)	9.40 (6.31)

Note: The Table shows means (standard deviations) of subjective anxiety ratings (anxiety), heart rate, log10-transformed high frequency heart rate variability (HF-HRV), and skin conductance level (SCL) during the experimental conditions in participants with generalized anxiety disorder (GAD) with and without major depressive disorder (MDD).