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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 the 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.

1. Introduction

Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are highly comorbid, as suggested by a number of epidemiological studies (Breslau et al., 1995; Kessler et al., 1996, 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 et al., 1999), 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 et al., 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.

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 et al., 1998; Zahn-Waxler et al., 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 and Davis, 1999) and worrying (Borkovec et al., 1998).

Worrying has been associated with reduced autonomic flexibility as a result of low cardiac vagal tone (Borkovec and Hu, 1990; Hoehn-Saric and McLeod, 2000; Hofmann et al., 2005; Lyonfields et al., 1995; Thayer et al., 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 et al., 2002; Hazlett-Stevens and Borkovec, 2001); for a review, see Friedman (2007). Similarly, the review of the depression literature on cardiac vagal tone has been mixed (Rottenberg, 2007).

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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 and Heimberg, 2002; Segerstrom and 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).

2. Method

2.1. 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%), χ^2 (1) = .07, p = 0.99; tricyclic antidepressants (8.00% vs. 0.00%), χ^2 (1) = 1.18, p = .53; benzodiazepines (24.00% vs. 0.00%), χ^2 (1) = 3.97, p = .07; contraception (20.00% vs. 28.57%), χ^2 (1) = .37, p = .70; stimulants (4.00% vs. 7.00%), χ^2 (1) = .18, p = .99, and analgesics (0.00% vs. 14.29%), and χ^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).

2.2. Diagnostic assessment

Diagnoses were established with the Anxiety Disorders Interview Schedule for DSM-IV: Lifetime version (ADIS-IV-L; DiNardo, Brown and 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 the 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 and 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 and 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).

2.3. 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, χ^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).

2.4. 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 and Borkovec, 1990) is a 16-item self-report questionnaire measuring the general tendency toward excessive worrying, without reference to a specific content. It shows very good reliability, convergent and discriminant validity (cf. Brown, Antony and Barlow, 1992), and treatment sensitivity (Borkovec and 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 et al., 1996b) 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 et al., 1996a) and has been shown to be a valid indicator of depression with good diagnostic discrimination (Dozois, Dobson, and Ahnberg, 1998).

2.5. Experimental procedure

As part of the laboratory experiment, which lasted approximately 30 min, 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