Research Article

IS GENERALIZED ANXIETY DISORDER AN ANXIETY OR MOOD DISORDER? CONSIDERING MULTIPLE FACTORS AS WE PONDER THE FATE OF GAD

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Generalized anxiety disorder (GAD) and major depressive disorder (MDD) demonstrate a strong relationship to each other at both genotypic and phenotypic levels, and both demonstrate substantial loadings on a higher-order negative affectivity factor [see Watson, 2005: J Abnorm Psychol 114:522–536]. On the basis of these findings, there have been a number of calls to reclassify GAD in the same category as MDD (the "distress disorders"). However, any consideration of the reclassification of GAD should also take into account a number of other factors not only related to GAD and MDD but also to the overlap of these disorders with other anxiety and mood disorders. First, GAD has established reliability and validity in its own right, and specific features (e.g., worry) may become obscured by attempts at reclassification. Second, examination of the nature of the overlap of GAD and MDD with each other and with other disorders suggests a more complex pattern of differences between these conditions than has been suggested (e.g., MDD has strong relationships with other anxiety disorders, and GAD may be more strongly related to fear than it may first appear). Third, although findings suggest that GAD and MDD may have overlapping heritable characteristics, other evidence suggests that the two disorders may be distinguished by both environmental factors and temporal presentations. Finally, although overlap between GAD and MDD is reflected in their relationships to negative affectivity, temporal relationships between these disorders may be demonstrated by functional changes in emotional responsivity. Depression and Anxiety 25:289–299, 2008. © 2008 Wiley-Liss, Inc.

INTRODUCTION

The past two decades have seen considerable advances in understanding and treating anxiety and mood disorders. However, despite the delineation of specific mechanisms (e.g., interoceptive sensitivity in panic disorder versus fear of negative evaluation in social anxiety disorder), high levels of comorbidity are the norm in clinical [Brown et al., 2001a] and community samples [Kessler et al., 2005b], which challenges the utility of these specific demarcations. Further, when multiple disorders are present, reliable diagnosis can be difficult. Particularly characteristic of

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this difficulty is generalized anxiety disorder (GAD), the nosological integrity of which has been criticized [for a review, see Mennin et al., 2004]. Although the reliability and validity of GAD have improved considerably because worry was established as its central feature, GAD exhibits high rates of comorbidity with unipolar mood disorders [see Brown et al., 2001a; Kessler et al., 2005b], which may reflect a shared genetic diathesis [e.g., Kendler et al., 1992].

Watson [2005, 2008] criticized the rationally derived diagnostic classification system in *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) [American Psychiatric Association ,1994] for categorizing disorders on the basis of shared phenomenological features rather than empirical data. He explained that this system assumes weak relationships across diagnostic categories (e.g., social anxiety disorder and dysthymia) and stronger relationships within a diagnostic category (e.g., social anxiety disorder and posttraumatic stress disorder) and, thus, cannot directly account for the high levels of comorbidity that often occur across diagnostic categories (e.g., between GAD and major depressive disorder (MDD)). Citing findings from epidemiological samples, he explained that the overlap between GAD and MDD is substantial [tetrachoric correlations between disorders range from .59 to .70; see Kessler et al., 2005b; overlap between these disorders is also high in clinical samples; see Brown et al., 2001a]. Further, he reviewed structural modeling studies that examined either symptom patterns or diagnoses [e.g., Brown et al., 1998; Krueger et al., 1999; Watson et al., 1995], finding a high degree of association between GAD and MDD, with both disorders loading most strongly on a higher-order factor of negative affectivity (i.e., neuroticism, distress). Watson reviewed genotypic data [e.g., Krueger RF, 1999] suggesting that GAD and MDD are virtually indistinguishable. Finally, Watson also noted that both conditions respond to treatment with serotonin and norepinephrine reuptake inhibitors, further suggesting a shared relationship between GAD and MDD.

Given this substantial overlap, some investigators have questioned whether GAD should be diagnosed independently of MDD in DSM-V. Proposed changes for DSM-V include (1) placing these disorders with dysthymia and posttraumatic stress disorder in a category of "distress disorders" [Watson, 2005], which would be distinguished from a "bipolar disorders" category (comprising bipolar I, II, and cyclothymia) and a "fear disorders" category comprising the remaining DSM-IV anxiety disorders (e.g., panic disorder, specific phobia, and social anxiety disorder) with the exception of obsessive compulsive disorder; (2) recategorizing GAD as a mood disorder [Vollebergh et al., 2001]; (3) subsuming GAD under MDD as a subtype similar to "agitated depression" [see Kendler et al., 1996]; or (4) using a broader category such as neuroticism to capture both disorders, with the purpose of increasing predictive power and accounting

for the overlap that is seen in genotypic and phenotypic investigations [Andrews, 1996]. The architects of DSM-V and leading mood and anxiety disorders researchers are currently reviewing these suggestions as an alternative to the position that GAD should continue to be classified as an anxiety disorder (for more information, see "*The Future of Psychiatric Diagnosis: Refining the Research Agenda* (Depression and Generalized Anxiety Disorder Research Planning Conference)"; http://www.dsm5.org/conference6.cfm).

Although GAD and the unipolar mood disorders are significantly related, removing GAD from the anxiety disorders may be premature for two main reasons. First, this decision may not fully reflect the complex relationship that GAD shares with both mood and anxiety disorders. Second, the decision to remove GAD from the anxiety disorders arises without fully accounting for the relationship between mood disorders and anxiety disorders other than GAD. In the remainder of this paper, we consider six issues that challenge the arguments and suggestions of Watson [e.g., 2005, 2008] as well as others who favor separating GAD from the other anxiety disorders. Specifically, we explore whether (1) arguments to remove GAD from the other anxiety disorders are predicated on misconceptualizations of the diagnostic integrity of GAD, which has actually established greater reliability and validity as a diagnostic category than credited; (2) the degree of comorbidity between MDD and GAD is not unique to GAD and may also reflect a tautology based on the symptoms chosen to define the disorders in DSM-IV; (3) structural findings regarding symptom clustering may reflect these symptom inclusion decisions and, thus, may be alternatively interpreted to support retaining GAD as an anxiety disorder through a delineation of the relationship of MDD with fear disorders and fear processes within GAD; (4) although GAD and MDD may share common genetic diatheses, environmental factors distinguish these disorders and may account for both similarities and differences in treatment efficacy; (5) given environmental influence in the expression of GAD or MDD, the examination of *functional* relationships between the disorders may provide a greater understanding of these disorders than reliance on structural relationships alone; and (6) rather than favoring "lumping" or "splitting," categorization can reflect both higher- and lower-order relationships, possible diatheses and stress factors, and the temporal relationship of these conditions if *both* structural and functional associations between the disorders are considered in nosological decisions regarding the overlap between GAD and mood disorders.

INTEGRITY OF THE DIAGNOSIS OF GAD

Many investigators cite the history of poor reliability of GAD as evidence for the need to reclassify. Other

common criticisms of GAD are that it is not associated with independent contributions to impairment or distress and that it lacks clear and specific mechanisms that could differentiate it from other conditions. Although early versions of GAD suffered considerably from low reliability and poor validity, GAD as defined in the DSM-IV has, to the contrary, achieved diagnostic reliability on par with other anxiety and mood disorders and demonstrated unique mechanisms and patterns of impairment.

RELIABILITY

Early investigations into the reliability of GAD provided little support for the diagnosis. Interrater reliability of GAD based on DSM-III [American Psychiatric Association, 1980] criteria was poor [κ = .47; DiNardo et al., 1983]. Reasons for low reliability may have included the lack of a clear marker for the condition and the inclusion of many nonspecific physical symptoms. However, worry became the essential feature of GAD in the DSM-III-R [American Psychiatric Association, 1987]. Sanderson and Barlow [1990] found that the presence of worry could be reliably detected, with a κ coefficient of .90. DSM-IV further clarified the diagnosis by focusing physical symptoms around chronic levels of tension and removing symptoms that more likely to reflect acute autonomic arousal. This change reduced rates of comorbidity with other anxiety disorders, increased the specificity of these physical symptoms [e.g., Joormann and Stöber, 1999; Marten et al., 1993], and improved interrater reliability of GAD (κ = .67 for current diagnosis), putting it on par with other disorders such as MDD [κ = .67 for current diagnosis; Brown et al., 2001b].

PREDICTIVE VALIDITY

Numerous studies demonstrate that GAD (with or without comorbid MDD) is associated with significant impairment and distress. Primary-care patients with noncomorbid GAD reported more disability days (in a 1-month period) and poorer social functioning than other primary-care patients [e.g., Ormel et al., 1994]. Kessler et al. [1999] examined the National Comorbidity Survey and the Midlife Development in the United States Survey and found that noncomorbid GAD and noncomorbid MDD had comparable rates of perceived mental health and social impairment and that these results were not due to co-occurring psychopathology or demographic variables. Wittchen et al. [2000] examined individuals assessed as part of the German National Health Interview and Examination Survey and found that groups with noncomorbid GAD, noncomorbid MDD, and co-occurring GAD and MDD had equivalently high levels of social and work impairment after controlling for demographic variables and other forms of psychopathology. Further, individuals with noncomorbid GAD reported poorer quality

of life than individuals with noncomorbid MDD. Stein and Heimberg [2004] reanalyzed data from the Ontario Health Survey Mental Health Supplement to determine the relative impact of each disorder in co-occurring GAD and MDD. The effects of GAD were examined while statistically controlling for the effects of MDD. Lifetime GAD was independently associated with an increased likelihood of dissatisfaction with the respondent's main activity and an increased likelihood of dissatisfaction with family life. Both past-year and lifetime GAD were significantly associated with an increased likelihood of low overall perceived well-being. Taken together, these investigations suggest that both GAD and MDD demonstrate significant, yet distinguishable, associations with impairment.

MECHANISM SPECIFICITY

Increases in reliability and delineation of the essential criteria for a diagnosis of GAD have led to the delineation of pathological mechanisms with greater specificity [see Borkovec et al., 2004]. Worry is more elevated in GAD than other anxiety and mood disorders [e.g., Chelminski and Zimmerman, 2003]. In addition, considerable evidence indicates that cognitive biases can differentiate GAD from MDD [for a review, see Mineka et al., 2003]. In particular, GAD, but not MDD, has shown strong associations with attentional biases to threatening stimuli. In contrast, memory biases are more common in MDD than GAD. Recently, other constructs have demonstrated patterns of specificity with GAD. Intolerance of uncertainty, which refers to one's characteristic difficulty with ambiguous and uncertain possibilities, has been found to be elevated in individuals with GAD compared to those with other anxiety and mood disorders, including MDD [see Dugas et al., 2004], although intolerance of uncertainty is also elevated in obsessive compulsive disorder [Holaway et al., 2006]. In contrast, individuals with MDD, but not GAD, appear to have a greater certainty that negative events will occur [e.g., Miranda and Mennin, 2007]. Emotion-related deficits have also differentiated GAD from MDD [Mennin et al., 2007]. In particular, GAD was uniquely related to greater emotional reactivity and dysregulation, when variance associated with MDD was constrained. In contrast, MDD had a specific relationship with poor ability to understand emotional information and negative beliefs about the consequences of experiencing emotions, when variance associated with GAD was constrained. Finally, although some biological mechanisms appear to be nonspecific (e.g., 5-HT system deficiencies), robust findings indicate a role of GABA/benzodiazepine receptor dysfunction in GAD, but not MDD [cf., Lydiard and Monnier, 2004].

DIAGNOSTIC CONVERGENCE

Structural models of diagnostic overlap have demonstrated that GAD and MDD load onto a higher-order

factor of generalized negative emotional distress (labeled "Anxious/Misery" or "Distress" in these studies) using both lifetime [Krueger et.al., 1999] and 12-month [Vollebergh et al., 2001] diagnoses. Further, in these studies, this factor was distinguished from a "Fear" factor on which panic disorder, agoraphobia, specific phobia, and social anxiety disorder loaded. However, a stronger test of the overlap between GAD and MDD comes from the examination of symptom sets rather than diagnoses, given that diagnoses are confounded by the categorization system from which they are derived [Brown and Barlow, 2005]. In studies examining symptom-level items related to anxiety and mood pathology [e.g., Watson et al., 1995], clusters of symptoms map onto three factors, which correspond to different aspects of emotionality, including heightened negative emotionality, reduced positive emotionality, and heightened autonomic arousal. Symptoms reflective of general anxiety and depressive symptoms both most strongly mapped onto negative emotionality, as in the diagnostic structural models, but only depressive symptoms mapped onto positive emotionality and only anxious symptoms mapped onto the autonomic arousal factor. One drawback to these symptom-level studies was the reliance on nonclinical samples. In contrast, Brown et al. [1998], examining both self-report symptom levels and diagnoses in a large patient sample, replicated findings that GAD and MDD factors (comprising both self-report and diagnostic data) shared an association with negative emotionality. Further, MDD and social anxiety disorder, but not GAD, were associated with low positive emotionality. In addition, GAD, but not MDD, was negatively related to autonomic arousal suggesting autonomic suppression [consistent with experimental findings in GAD; see Borkovec et al., 2004].

These findings not only support the relationship between GAD and MDD but also demonstrate important areas of divergence that should give us pause before making classification decisions based on structural overlap. First, the specificity of the relationship between GAD and MDD appears to be affected by the nature of inputs to the structural models, which reflect a tautology given the considerable symptomatic overlap in the DSM-IV criteria for these disorders. In addition, the findings from Brown et al. [1998] concerning the convergence of MDD and social anxiety disorder in relation to low positive affectivity as well as other sources reviewed below suggest a significant relationship between mood disorders and anxiety disorders other than GAD. Finally, the relationship of autonomic suppression to GAD, but not MDD, in the Brown et al. [1998] study, as well as other findings reviewed below concerning the role of fear in GAD, suggest that fear processes may be important in GAD but obscured by compensatory mechanisms such as worry. These points are expanded on herein.

SYMPTOMATIC OVERLAP BETWEEN GAD AND MOOD DISORDERS

Although the diagnostic structural analyses [Krueger et al., 1999; Vollebergh et al., 2001] reflecting the loadings of GAD and MDD on a higher-order factor were most robust, symptom-based structural models have been equivocal, with some showing superiority when GAD and MDD are combined in latent factors [e.g., Watson et al., 1995] and another showing superior fit when these disorders are kept separate [Brown et al., 1998]. One explanation for these heterogeneous results is the nature of the inputs submitted for modeling. Models limited to DSM-IV diagnoses or symptom clusters were most likely to find structural harmony for GAD and MDD. However, such inputs to the model are highly related by design (i.e., overlap between GAD and MDD may be partially a product of poor measurement of the distinction between the conditions). In contrast, Brown et al. [1998] utilized DSM-IV diagnoses and symptoms as well as additional measures of closely related processes such as worry [Penn State Worry Questionnaire; Meyer et al., 1990] and social interaction anxiety [Social Interaction Anxiety Scale; Mattick and Clarke, 1998]. Similarly, other analyses examining the overlap between mood and anxiety symptoms have shown greater distinctiveness in the conditions when anxious apprehension, assessed with the Penn State Worry Questionnaire, was included [e.g., Heller and Nitschke, 1998].

Although the diagnostic criteria for GAD in the DSM-IV reduced rates of comorbidity with other anxiety disorders and increased the specificity of its physical symptoms [e.g., Marten et al., 1993], they subsequently increased its overlap with MDD. Undoubtedly, the entities of "GAD" and "MDD" are both related to negative affectivity. Indeed, the emotions of fear/anxiety and sadness, the essential phenomenological ingredients of anxiety and unipolar mood disorders, have also been shown to map onto higher-order factors of negative affectivity [see Watson, 2005, 2008]. However, defining GAD and MDD using highly overlapping symptoms may obscure important distinctions between these disorders as well. A quick look at the diagnostic criteria for GAD reveals that four out of the six associated physical symptoms (i.e., restlessness, fatigue, difficulty concentrating, sleep difficulties) are also part of the diagnostic criteria for MDD. In addition, four of the symptoms required for MDD (i.e., sleep difficulties, psychomotor agitation, fatigue, difficulty concentrating) overlap with GAD. Similarly, three of the symptoms of dysthymia (i.e., sleep difficulties, fatigue, difficulty concentrating) also overlap with GAD. Given that three of these symptoms are required for GAD, five for MDD, and two for dysthymia, there is a high likelihood that individuals could meet criteria for GAD or a mood disorder with symptoms fully reflective of GAD (and

vice versa). Thus, it remains a question as to whether individuals who meet criteria for these diagnoses with overlapping symptoms are best described as having GAD, MDD, or both.

Brown et al. [2001b], noting the prominent overlap of GAD and MDD, suggested that GAD could be further refined to promote better separation from the mood disorders. Indeed, examinations of the six retained physical symptoms of GAD have shown discriminant validity between GAD and the other anxiety disorders but have not discriminated strongly between GAD and MDD [e.g., Joormann and Stöber, 1999; Kubarych et al., 2005]. Joormann and Stöber [1999] explored the ability of DSM-IV symptoms of GAD to discriminate depressive symptomatology from worry. Although the majority of current symptoms of GAD were not well differentiated from depression, muscle tension appeared to be uniquely related to worry and difficulty concentrating appeared to have a particularly strong relationship with depression. Indeed, muscle tension was negatively related to depression in this study. Kubarych et al. [2005] also found muscle tension, but not other DSM-IV symptoms of GAD, to be unique to the disorder in a factor analysis of a large sample of female twins. These findings of the specificity of muscle tension to GAD are noteworthy given that physiological studies have also found differences between GAD and healthy controls [e.g., Hoehn-Saric et al., 1989]. One might question whether muscle tension was emphasized and difficulty concentrating de-emphasized, whether the patterns of co-occurrence between GAD and MDD might be altered.

Other symptoms, not currently included in the DSM-IV criteria for GAD and MDD, might help to further differentiate these disorders. Intolerance of uncertainty [Dugas et al., 2004] and subjective emotional reactivity [i.e., affect intensity; Mennin et al., 2007] are two possible candidate symptoms. Preliminary findings suggest that the inclusion of one item inquiring about intensity of emotional responses increases distinctiveness of GAD in relation to MDD. Another possibility for increasing distinctiveness of GAD is to alter what might be overly restrictive criteria in the current symptom set. Ruscio et al. [2005] found that when worry was not required to be excessive to meet criteria for GAD, comorbidity with MDD and dysthymia decreased, although GAD without excessive worry remained comparable to the original diagnosis in persistence, impairment, treatment-seeking, and family aggregation. Further, Kessler et al. [2005a] found a similar result when the duration of GAD was reduced from 6 months to 1 or 2 months. One possibility that has been offered by Kessler et al. [2004] for the high comorbidity of GAD is its low prevalence in comparison to MDD, which might inflate co-occurrence of disorders given less variance available for heterogeneity. It may be that decreasing arbitrarily restrictive criteria increases prevalence rates (as both of these

criteria changes did) and, subsequently, decreases the effect of comorbidity. Interestingly, bipolar II comorbidity did not decrease as a result of the duration change in the Kessler et al. [2005a] study. This argument is consistent with a recent analysis of the comorbidity rates of bipolar disorders in the National Comorbidity Survey Replication , which demonstrated a strong relationship of both bipolar I (39%) and bipolar II (37%) disorders with GAD, and a study of comorbidity in a Hungarian epidemiological sample in which rates of comorbidity with GAD were higher in bipolar II disorder (21%) than MDD [14%; Rihmer et al., 2001]. These results suggest that classification of GAD and the mood disorders should reflect relationships with bipolar as well as unipolar mood disorders. Despite these encouraging possibilities for modifying GAD criteria, its important to also note that some changes might lead to increases in the overlap between GAD and MDD, such as lifting the hierarchical requirement between the conditions (i.e., GAD cannot be diagnosed when MDD is temporally overlapping), which has been shown to increase rates of GAD in individuals with MDD [Zimmerman and Chelminski, 2003].

SYMPTOMATIC OVERLAP BETWEEN MDD AND OTHER ANXIETY DISORDERS

Although GAD and MDD are highly overlapping in epidemiological [Kessler et al., 2005b] and clinical [Brown et al., 2001a] samples, these same sources of data also show strong relationships between the unipolar mood disorders and the "fear disorders" such as social anxiety disorder and panic disorder. For example, MDD was highly related to GAD (tetrachoric correlation of .62) but also showed strong relationships to panic disorder (.48), agoraphobia (.52), social anxiety disorder (.52), and specific phobia (.43) in the National Comorbidity Survey Replication. With dysthymia, the correlations with GAD and other anxiety disorders are almost indistinguishable. Tetrachoric correlations with dysthymia were equivalent for GAD (.55), social anxiety disorder (.55), and panic disorder (.54) and were only slightly lower for specific phobia (.44) and agoraphobia (.44). Slade and Watson [2006] analyzed epidemiological data from the Australian National Survey of Mental Health and Well-Being and found similar tetrachoric correlations between the mood disorders and other anxiety disorders (correlations ranged from .50 to .56). Analysis of data from the clinical sample of Brown et al. [2001a] produced similar patterns of overlap between MDD and the other anxiety disorders. Rates of co-occurrence between MDD and GAD (57% with hierarchy rules lifted) were not greatly different than the rates with social anxiety disorder (43%) or panic disorder with or without agoraphobia (46%). For dysthymia, the rates of overlap with GAD were comparable to social anxiety disorder (56%) but higher than panic disorder with or

without agoraphobia (34%). Interestingly, panic disorder with agoraphobia ($\beta = .65$) loaded on the negative affectivity higher-order factor to almost the same degree as MDD ($\beta = .67$) in the Brown et al. [2001b] structural equation modeling study. Similarly, using the data from the original National Comorbidity Survey , which utilized DSM-III-R criteria, Weinstock and Whisman [2006] found that noncomorbid GAD and noncomorbid panic disorder did not differ significantly in rates of neuroticism (i.e., negative affect), but pure MDD had considerably lower rates.

Another consideration in pondering the overlap of mood disorders with other anxiety disorders versus GAD is the role of positive affectivity in MDD and social anxiety disorder. A strong relationship has been found between MDD and reduced positive affectivity [e.g., Watson et al., 1995]. Similarly, a diminished response to positive stimuli in MDD has also been demonstrated in experimental settings using subjective, expressive, and psychophysiological indices [e.g., Rottenberg et al., 2002]. A recent meta-analysis [Bylsma et al., 2008] of laboratory studies found that, although individuals with MDD were characterized by reductions in emotional reactivity to both positively and negatively valenced stimuli, effects were stronger for positive stimuli ($d = -.53$) than for negative stimuli ($d = -.25$). However, low positive affectivity does not appear to be specific to MDD. In the Brown et al. [1998] structural equation model, GAD did not demonstrate a relationship with positive affectivity, but both MDD and social anxiety disorder did (β's of $-.29$ and $-.28$, respectively).

Kashdan [2007] provided theoretical and empirical support for the unique role of low positive affectivity in social anxiety disorder. In a meta-analysis of 34 studies, social anxiety was significantly negatively associated with positive affectivity ($r = -.36$) and curiosity ($r = -.24$), a trait associated with appetitive motivation. Further, these associations remained significant after controlling for depressive symptoms or diagnoses (r's $= -.21$ for both positive affectivity and curiosity). Kashdan interprets these meta-analytic findings within a self-regulatory framework. He suggests that excessive self-evaluative concern may lead to avoidant regulatory actions in service of anxiety reduction that interfere with reward and promotion behaviors. Similar to behavioral perspectives on depression [e.g., Libet and Lewinsohn, 1973], if an individual withdraws from a potentially rewarding context due to avoidance, the likelihood of future rewarding circumstances might diminish. However, one might expect that the reasons for withdrawal from rewarding contexts might be different for social anxiety (i.e., avoidance of perceived threat) than for depression (i.e., decreased value of volitional processes of the reward stimulus). Nonetheless, it appears that the decreased positive emotions, not central to GAD, are an important component of both social anxiety disorder and depression. Consistent with these findings, Mennin et al. [2007] found that

MDD and social anxiety, accounting for each other's variance as well as that of GAD, were both characterized by a poor understanding of emotions and negative beliefs about the consequence of emotions, including positive affect. Interestingly, when MDD and social anxiety were controlled, GAD showed no relationship to these emotion variables, suggesting that social anxiety and MDD may share a broader pattern of emotional characteristics involving regulatory responses to emotions in addition to levels of emotional experience (i.e., reduced positive affectivity).

SYMPTOMATIC OVERLAP BETWEEN GAD AND OTHER ANXIETY DISORDERS: IS THERE FEAR WITHIN GAD?

Removing autonomic symptoms from the criteria for GAD in DSM-IV increased specificity with the other anxiety disorders [e.g., Marten et al., 1993] but may have also led to the obfuscation of the role of fear processes in generalized anxiety and worry. Despite the removal of autonomic symptoms, DSM-IV GAD was highly correlated with "fear disorders" including panic disorder (.46), agoraphobia, (.45), and social anxiety disorder (.47) in the National Comorbidity Survey Replication [Kessler et al., 2005b]. These correlations were similar to the association found for social anxiety disorder and panic disorder (.48). In the Australian National Survey of Mental Health and Well-Being sample, Slade and Watson [2006] found similarly high tetrachoric correlations for GAD and panic disorder (.62), agoraphobia (.61), and social anxiety disorder (.58), which were not well distinguished from the associations between social anxiety disorder and panic disorder (.59). Consistent with these reported rates, Maier et al. [2000] examined the role of the autonomic symptoms that comprise the diagnosis of GAD in ICD-10 (but were removed from DSM-IV) and found that there were strong relationships between these symptoms and persistent worry and anxiety. These relationships suggest that, at least for a subgroup of individuals with GAD, fear processes may be an important component of their anxious presentation. Indeed, despite the formal removal of the autonomic symptoms from the DSM-IV criteria set, limited symptom panic attacks are often seen clinically in patients with GAD.

In contrast to the increased autonomic activity demonstrated by these associations, Brown et al. [1998] demonstrated that, whereas panic disorder was positively associated with an autonomic arousal factor, GAD was *negatively* associated with this same factor. Interestingly, MDD and social anxiety disorder were not significantly related to this factor, providing further support for a more complex relationship among GAD, MDD, and social anxiety disorder than previously thought. But how can we explain positive correlations between "fear disorders" (e.g., panic disorder) and GAD in the context of an inverse structural relationship? The

answer likely lies in the function of worry in GAD. As mentioned above, Brown et al. [1998] used multiple self-report and diagnostic indices to represent GAD, including the Penn State Worry Questionnaire and other process measures of worry. This greater focus on worry may account for the negative relationship with autonomic arousal. In numerous studies, worry has been related to autonomic inflexibility in GAD [e.g., see Borkovec et al., 2004; Hoehn-Saric et al., 1989]. Borkovec and colleagues have developed one of the most prominent and well-supported models of worry in GAD. This model asserts that worry serves an avoidant function by suppressing autonomic hyperarousal. This functional relationship has been repeatedly demonstrated, and there would be little to suppress if persons with GAD did not cycle through periods in which they were overwhelmed by these symptoms. Most likely, worry is enacted, in part, as a response to autonomic activity, to which individuals with GAD have reported to have more sensitivity than other individuals [i.e., anxiety sensitivity; see Rector et al., 2006]. Thus, autonomic activity may be obscured by the engagement of worry. Further support for this functional relationship between autonomic activity and worry comes from the established clinical finding of "relaxation-induced anxiety," in which patients with GAD engaged in relaxation-encouraging exercises (e.g., progressive muscle relaxation; diaphragmatic breathing) experience a surge in autonomic activity, often experienced as a limited symptom panic attack [see Heide and Borkovec, 1983].

Although speculative, the notion that worry serves as a compensatory mechanism could also be gleaned from the developing neurobiological literature. For example adults with GAD evidence elevated levels of dorsolateral prefrontal cortical activation [Mathew et al., 2004]. This area is typically associated with effective executive control of negative emotions yet it is showing increases in symptomatic individuals with GAD—potentially showing a compensatory mechanism at play. Interestingly, children and adolescents with GAD, who presumably do not have the same level of cognitive function, do not display this same level of dorsolateral prefrontal activation but do display elevated amygdalar activity [i.e., suggestive of fear processes; DeBellis et al., 2000; McClure et al., 2007]. It may be that, as individuals with GAD get older and their cognitive abilities get stronger, they rely more on worry, as Borkovec would suggest, to constrain fear responses. Worry may be reinforced by fear reduction, suggesting that although it may be obscured, fear still plays an important motivational role in GAD.

ETIOLOGIC CONVERGENCE

Delineation of temperamental markers reflective of a higher-order personality factor (i.e., neuroticism, negative affectivity) that are reliable, predictive of psychopathology, and associated with identifiable biological markers [e.g., human serotonin transporter gene, SLC6A4; see Hariri et al., 2002] have clear value to our etiological understanding of the anxiety and mood disorders. However, they are unlikely to fully account for all phenotypic presentations of these disorders, even ones most strongly related to higher-order personality factors such as GAD and MDD. Despite the robust and similar heritability ratings for these disorders, numerous environmental and developmental factors distinguish their expression. Further, the proximal etiologic relationship between GAD and MDD is likely a temporally functional one with GAD more likely to precede MDD. Thus, rather than focusing exclusively on structural relationships between these disorders, examinations of the functional emotional relationships between GAD and MDD may elucidate how these disorders converge and diverge.

DIATHESIS OVERLAP

Meta-analytic investigations of familial and genetic factors demonstrate that GAD and MDD are associated with moderate levels of heritability [37 and 32%, respectively; Hettema et al., 2001; Sullivan et al., 2000]. Family studies have demonstrated that rates of GAD are elevated in first-degree relatives of both GAD and MDD probands [e.g., Kendler et al., 1997]. Further, Kendler et al., [1992] have demonstrated strong heritability relationships between GAD and MDD . These studies consistently show that genetic factors are almost entirely shared between these disorders, but shared environmental variance is quite modest. Mineka et al. [1998] suggested that this shared genetic factor likely reflects individual differences in general distress and negative affectivity. Indeed, studies indicate that neuroticism is highly genetically related to both GAD [Hettema et al., 2004] and MDD [Fanous et al., 2002], with a stronger effect for GAD. However, the genetic overlap between GAD and MDD is only moderately related to the genetic overlap of neuroticism with each disorder [e.g., Hettema et al., 2006], suggesting that, even at the genetic level, other factors beyond dispositional emotionality may account for the shared inheritance of GAD and MDD. Consistent with these genetic data, measures of emotionality such as neuroticism have been found to predict comorbidity patterns in these disorders [e.g. Chambers et al., 2004], yet a significant number of individuals with elevations on these dispositional variables do not have GAD or MDD [e.g., Rettew et al., 2006]. Further, Kessler et al. [2004] warned that these results should be interpreted with caution, because models in these studies assume that the joint effects of genes and environment are additive and, thus, ignore genetic influence on environment. Likely, the role of genotypic variables in GAD and MDD are heterogeneous as are their effects on phenotypic presentations. More research is clearly needed to delineate how genetic factors in GAD, MDD, and neuroticism may interact and influence phenotypic expression.

STRESSOR DISTINCTIONS

Various stressors (e.g., traumatic events, loss) may interact with the same diathesis (e.g., heritable factors) to produce different outcomes. Indeed, although genetic studies demonstrate strong relationships between GAD and MDD, environmental factors appear to diverge to a greater degree [e.g., Kendler et al., 1992]. Few studies have examined patterns of environmental factors between DSM-IV diagnoses of GAD and MDD. However, recently, Moffitt et al. [2007] examined risk factors associated with noncomorbid GAD, noncomorbid MDD, and comorbid MDD and GAD in the 1972–1973 Dunedin birth cohort of 1,000 individuals followed to age 32 (with 96% retention). Individuals with noncomorbid GAD demonstrated a discernable pattern of stressors (i.e., maltreatment, low SES, childhood behavior problems) compared to individuals with only MDD (family history of depression, low positive emotionality). Further, the MDD-only group showed less severe stressors than the comorbid MDD and GAD group, whereas the GAD-only group did not, suggesting that the presence of GAD may impart a greater risk for severity despite common genotypic influences of the disorders. Further, Kendler et al. [2003] found that types of life events differentially predicted MDD and GAD (using a 2-week minimum duration) in 7,322 male and female twins from the Virginia Twin Registry. Humiliation events predicted pure MDD, but not pure GAD. In contrast, danger events predicted pure GAD, but not MDD. However, most events characterized by loss were nonspecific with the exception of death and respondent-initiated separation from significant others, which were specific for pure depressive episodes.

THE FUNCTIONAL RELATIONSHIP BETWEEN GAD AND MDD

Given the differences in environmental stressors between GAD and MDD, it is important to determine when these disorders appear similar in emotional characteristics and when they diverge over time. Cuthbert [2005] pointed out that it is unclear how hierarchical models can discern mechanisms of change in diagnostic phenomena over time from structural data, which are static by definition (i.e., dispositional emotionality). Brown [2007] provided a notable exception to this assertion with an examination of structural data over time using latent growth modeling to determine the relationship between temperamental stability and disorder influence over a 2-year period in a clinical sample. Temporal covariation of GAD and MDD was low ($r = .30$) and actually less than that of social anxiety disorder and MDD ($r = .54$), suggesting that these disorders do not occur largely in synchrony over time. However, the temporal overlap between GAD and MDD was explained primarily by their shared relationship to negative affectivity. Further, initial levels of negative affect accounted for a stable,

unremitting course in both GAD and MDD. Thus, negative affectivity appears to play a role, yet cannot fully account for, the temporal presentations of GAD and MDD.

A focus on structural emotional vulnerability factors may obscure *functional* relationships between emotional phenomena in GAD and MDD. GAD typically onsets earlier to the onset of an MDD episode, and the presence of GAD increases the likelihood of a later MDD episode to a greater degree than any other anxiety disorder [see Kessler et al., 2004]. These results suggest a possible functional relationship between GAD and MDD, such that characteristics of GAD may increase the likelihood of the characteristics of MDD. Sole focus on the structure of emotion may obscure the mechanisms by which emotional features determine when someone expresses GAD versus MDD or how, over time, GAD may lead to MDD. Indeed, despite the high overlap in structural negative affect, GAD and MDD appear to exhibit surprisingly distinct patterns of emotional reactivity in laboratory settings. In a review Rottenberg [2005] had demonstrated that individuals with a current episode of MDD are characterized by a blunted emotional response to both positive and negative emotional stimuli, which they have termed *context insensitivity* to emotions. In contrast, Mennin et al. [2005, study 3] and McLaughlin et al. [2007] have found *hyperreactivity* to various emotional contexts in individuals with GAD. Thus, although these disorders share an increased likelihood for negative affect, they may be distinguished by differences in shorter duration fluctuations in emotional response as represented by either graded (i.e., GAD) or flattened (i.e., MDD) peaks and valleys in the overall landscape of their temporal emotion presentation [Rottenberg, 2005]. Changes from heightened emotional reactivity to blunted emotional response may provide a marker for mechanisms by which GAD leads to an MDD episode. Possible mechanisms for these changes in emotional reactivity include functional changes from extreme goal focus to motivational disengagement [see Johnson, 2005], from uncertainty to certainty about the negativity of future events [e.g., Dugas et al., 2004; Miranda and Mennin, 2007] or from beliefs of helplessness to beliefs of hopelessness [see Alloy et al., 1990]. Delineation of the role of emotion reactivity may not only elucidate mechanisms through which GAD increases the likelihood of a subsequent episode of MDD but also help inform the best approach to categorizing these disorders (i.e., accounting for both structural overlap and functional distinction) and, inevitably, inform treatment of individuals suffering with both mood and anxiety difficulties.

CONCLUSION

There have been numerous calls to restructure classification of disorders in DSM-V [e.g., Watson,

2005; Widiger and Clark, 2000]. Dimensional constructs such as neuroticism or negative affect account for sizable portions of variance in the anxiety and mood disorders and, thus, may provide a fruitful alternative to the current nosological structure, which suffers from poor distinctiveness among categories and high levels of comorbidity. In particular, GAD and MDD demonstrate significant overlap in genotype and phenotype and relationships with higher-order negative affectivity [see Watson 2005, 2008]. On the basis of these findings, there have been a number of calls to reclassify GAD to reflect overlap with MDD. However, considerations to reclassify GAD should take into account a number of factors related to GAD, MDD, and their overlap with other anxiety and mood disorders. First, GAD has established reliability and validity in its own right, and specific features (e.g., worry) may be obscured by attempts at reclassification. Second, examination of the overlap of GAD and MDD with each other and with other disorders suggests a more complex pattern of differences between these conditions than has been suggested (e.g., MDD has strong relationships with other anxiety disorders, and GAD may be more strongly related to fear than it may first appear). Third, although findings suggest that GAD and MDD may have overlapping heritable characteristics, other evidence suggests that the two disorders may be distinguished by environmental factors and temporal presentations. Further, whereas dispositional overlap between GAD and MDD is reflected in their relationships to negative affectivity, temporal relationships between these disorders may be demonstrated by functional changes in emotional responsivity.

These assertions suggest a more complex picture of the relationship between anxiety and mood disorders than suggested by Watson [2005, 2008]. Although there is a clear need to consider dimensional classification and the inclusion of higher-order emotionality factors that reflect underlying genetic processes, reliable differences support current distinctions in the classification of specific mood and anxiety disorders. One may see this issue as a classic "lumper" versus "splitter" debate with both approaches having merit. However, it is difficult to determine how both general and specific categories could be accounted for in DSM-V. Watson [2005, 2008] and others [e.g., Krueger et al., 1999] provide a compelling model for restructuring classification to account for both higher-order characteristics and lower-order category relationships. However, given possible complexities in the overlap of GAD and MDD with each other and with other anxiety and mood disorders, alternative frameworks deserve consideration. One possibility is that anxiety and mood disorders could be diagnosed on three levels. Rather than separating certain anxiety and mood disorders or all anxiety and mood disorders from each other, specific diagnoses of "emotional disorders" could be given at the lowest level of any of the existing categories. At the next level, individuals could be diagnosed according to positive or negative relationships with structural emotional characteristic factors such as negative affectivity (indicated by avoidance and inhibition), positive affectivity (indicated by appetitive and exploratory motivation), and physiological hyperarousal (indicated by heightened reactivity in autonomic indicators). However, unlike Watson's approach, this level of diagnosis need not be orthogonal to lower-order categories. In other words, positive affectivity could relate negatively to both MDD and social anxiety disorder; negative affectivity could relate positively to MDD, GAD, and panic disorder [given findings from Brown et al., 1998], and physiological hyperarousal could positively indicate panic disorder and negatively indicate GAD. At the highest level, one could also be diagnosed solely by an internalizing factor, which captures the overlapping relationships of all anxiety and mood disorders. This system would also allow examination of lower-order relationships within a higher-order category (e.g., relationship between course of GAD and MDD in a sample of those meeting criteria for "negative affectivity"). Classification changes in DSM-V will need to be empirically evaluated, and changes that provide the greatest amount of unique information are to be preferred. Nonetheless, nosological changes to DSM-V that simultaneously account for *both* overlap and distinctiveness in disorders such as GAD and MDD may best help advance our understanding of convergent and divergent symptom presentations.

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