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Investigating the nature of co-occurring depression and anxiety: Comparing diagnostic and dimensional research approaches

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Abstract

Background—Although approximately half of adults diagnosed with a depressive or anxiety disorder exhibit their simultaneous co-occurrence, traditional research has centered on single-target diagnoses, overlooking comorbidities within samples. In this article, we review and extend the literature that directly investigates co-occurring depression and anxiety, with the goal of shifting the focus from co-occurring diagnoses to symptom dimensions.

Methods—First, we review studies that have directly compared psychobiological features (neural, neuroendocrine, autonomic) across depression, anxiety, and their co-occurrence, defined either categorically or dimensionally. Second, we analyze adults' diurnal cortisol secretion to examine the independent and interactive relations of continuously-assessed depressive and anxiety symptoms to neuroendocrine function.

Results—Previous findings on the psychobiology of diagnostic co-occurrence are mixed. While nascent, evidence from dimensionally focused studies suggests that co-occurring levels of depressive and anxiety symptoms can interact with one another, as reflected in a distinct psychobiological profile for individuals with high levels of both symptom dimensions. Results of our analyses support this formulation: we found that depressive and anxiety symptom dimensions interacted consistently in their relation to the measures of diurnal cortisol.

Limitations—The illustrative sample was relatively small and included only women; future research should examine generalizability of these findings.

Conclusions—A dimensional approach to investigating the psychobiology of co-occurring depression and anxiety affords both conceptual and practical advantages. Simultaneously assessing depressive and anxiety symptom dimensions can efficiently capture their unique, shared, and interactive features, thereby identifying targets for intervention across a wide range of symptom presentations.

Keywords

Depression; Anxiety; Comorbidity; Symptom dimension; Cortisol

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1. Introduction

Depressive and anxiety disorders have among the highest rates of comorbidity of all psychiatric diagnostic categories (Kessler et al., 2005; reviewed in Mineka et al., 1998). Their comorbidity is particularly striking in rates of current co-occurrence: 45–67% of individuals diagnosed with a unipolar depressive disorder meet criteria for at least one concurrent anxiety disorder, and 30–63% of individuals diagnosed with an anxiety disorder meet criteria for concurrent unipolar depression (Brown et al., 2001; Fava et al., 2000; Lamers et al., 2011). This form of co-occurrence is associated with a more severe and protracted clinical course, greater disability, and higher risk for suicide than is either category of disorder alone (Ballenger et al., 2001; Bruce et al., 2005; Fava et al., 2006; Kessler et al., 1999; Lamers et al., 2011; Roy-Byrne et al., 2000; Seo et al., 2011; van Balkom et al., 2008). It is perhaps not surprising, therefore, that persons with co-occurring depression and anxiety are more likely to utilize mental health care services than are their counterparts who have either condition alone (Kessler et al., 2015; McLaughlin et al., 2006). Unfortunately, however, co-occurring depression and anxiety is also more refractory to front-line psychosocial and pharmacological treatments than are non-co-occurring forms of these disorders (Bagby et al., 2002; Domschke et al., 2010; Erwin et al., 2002; Fava et al., 2008; van Balkom et al., 2008; Wittchen et al., 2002).

In attempting to explain these high rates of comorbidity, theorists have proposed shared etiologies or vulnerability factors at various units of analysis (e.g., genes, temperament, personality) that lead individuals to be diagnosed with both depressive and anxiety disorders over their lifetime (e.g., Barlow, 2002; Clark et al., 1994; Kendler et al., 1992). Some investigators have also suggested that certain disorders, most notably Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD), co-occur at a single point in time, in part because of symptom overlap in their diagnostic criteria (Hunt, 2000; Zbozinek et al., 2012). Despite this rich literature focusing on the *causes* of co-occurrence, however, no formulation has yet characterized the *nature* of the co-occurring pathology. That is, how do persons with co-occurring depression and anxiety compare to persons with ‘purer’ diagnoses with respect to pathophysiology? Of course, several theoretical models outline distinguishing features for each single category of disorder, such as anhedonia (specific to depression), physiological hyperarousal (specific to anxiety disorders; e.g., Clark and Watson, 1991), and different neural (e.g., Davidson, 1992; Heller, 1993) and cognitive (e.g., Mathews and MacLeod, 2005) substrates for depression and anxiety. Extant models stop short, however, of describing precisely how these processes combine in co-occurring presentations (see this issue raised in Heller et al., 1995; Ionescu et al., 2013; Mineka et al., 2014; Shankman and Klein, 2003). For example, do individuals with co-occurring depression and anxiety exhibit in an additive fashion the abnormalities that have been associated with each disorder independently? Or, do symptoms or diagnoses of depression and anxiety interact more dynamically with one another, as manifested by a distinct profile of psycho-biological functioning in co-occurrence that is not simply the sum of its parts? This gap in our knowledge about co-occurrence is due to the focus of traditional research in both psychology and psychiatry on single-target diagnoses, typically ignoring or excluding comorbidities within samples (reviewed in Beuke et al., 2003; Ingram and Hamilton, 1999).

Increasing our understanding of the nature of co-occurring depression and anxiety is critical for advancing theories of comorbidity and for developing more effective and personalized treatments for the substantial proportion of patients who have co-occurring symptoms and disorders.

1.1. Aims and scope of this article

In this article, we present conceptual models of the nature of psychiatric co-occurrence and review current empirical evidence concerning neural, neuroendocrine, and autonomic functioning in co-occurring depression and anxiety, first from a diagnostic framework and then from a dimensional perspective. This evidence leads us to advocate taking a dimensional research approach to the study of co-occurrence. In this context, we use an original dataset to illustrate the utility of this method. Specifically, we analyze the relations of continuously-assessed depressive and anxiety symptoms to diurnal cortisol as an index of hypothalamic-pituitary-adrenal (HPA)-axis functioning, a core psychobiological measure that features prominently in the dimensionally-focused National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) (http://www.nimh.nih.gov/research-priorities/rdoc/research-domain-criteria-matrix.shtml). Finally, we discuss more broadly the advantages of taking a dimensional approach to investigating the unique, shared, and interactive features of depression and anxiety.

2. Categorical approach to co-occurrence

Diagnostic co-occurrence is a complex research problem. Illustrating this complexity, Fig. 1 presents a visual depiction of the multiple diverse psychobiological profiles that may be observed in co-occurring depression and anxiety disorders, profiles that we label as ‘additive, ’ ‘average,’ ‘single-disorder dominant,’ ‘distinctive,’ and ‘shared,’ on the basis of the presumed features of each disorder alone. Here, ‘additive’ refers to profiles in which individuals with co-occurring diagnoses exhibit psychobiological features that are associated with both of the pure disorders in an additive manner (e.g., exhibiting the neural anomalies that are observed both in pure depression and in pure anxiety). ‘Average’ refers to individuals with co-occurring diagnoses exhibiting patterns of psychobiological functioning that are ‘in between’ those for the two pure disorders (e.g., a level of regional neural activation that is in between those shown in pure depression and pure anxiety). In contrast, ‘single-disorder dominant’ refers to individuals with co-occurring diagnoses exhibiting the features shown by individuals who are diagnosed with only one of the pure disorders (e.g., only the neuroendocrine pattern that is shown in anxiety alone, and not the pattern that is shown in depression alone). ‘Distinctive’ reflects profiles in which individuals with co-occurring diagnoses exhibit unique psychobiological features that are not apparent in either of the pure disorders (e.g., a neuroendocrine pattern that is not shown in either depression alone or anxiety alone). Finally, ‘shared’ refers to individuals with both pure and co-occurring diagnoses exhibiting common psychobiological features (e.g., levels of autonomic activity that are consistent across depression alone, anxiety alone, and co-occurring anxiety and depression).

In attempts to gain traction in addressing this complexity, several studies have directly compared psychobiological functioning in individuals diagnosed with co-occurring versus non-*co*-occurring depression and anxiety disorders. Below, we review these studies that have used a four-group design to compare diagnoses (depressive disorder alone, anxiety disorder alone, co-occurring depression and anxiety disorder, and non-psychiatric control), which is necessary in order to draw conclusions about the unique, shared, and interactive features of these disorders. Only three such studies have assessed cortisol functioning, the focus of our sample data analysis. Therefore, to provide a broader context for understanding the psychobiology of co-occurrence, we also summarize studies of neural and autonomic functioning. Because a mixture of specific diagnoses has been examined both within and across studies, we organize the findings by level of analysis (neuroendocrine, neural, autonomic); whenever possible within each level of analysis, we organize the findings by diagnosis.

2.1. Neuroendocrine functioning

In the first study to assess cortisol in diagnostic co-occurrence, Young et al. (2004) examined HPA-axis responses to a laboratory social stressor, quantified via adrenocorticotropic hormone (ACTH) and cortisol reactivity. The clinical participants were diagnosed with MDD alone, an anxiety disorder alone (Social Anxiety Disorder [SAD], Panic Disorder [PD], or Posttraumatic Stress Disorder [PTSD]), and co-occurring MDD-anxiety disorder (SAD, PD, or PTSD; of note, co-occurrence only needed to be met within the past year). Relative to non-psychiatric control participants, those with co-occurring MDD-anxiety disorder exhibited elevated ACTH reactivity to the stressor, whereas those with either MDD alone or an anxiety disorder alone did not. Group differences in cortisol reactivity were in the same direction but slightly weaker. Together, these findings indicate a distinctive neuroendocrine profile for co-occurrence that is not shown in either disorder alone. In this same sample, Cameron et al. (2004) assessed growth hormone (GH) response to clonidine as an index of noradrenergic functioning. Participants with an anxiety disorder alone and with co-occurring MDD-anxiety disorder showed equivalently blunted GH responses compared to control participants; participants with MDD alone did not differ from controls. Thus, even within the same sample, the profile for co-occurrence appears to diverge across response channels, indicating distinctive (Young et al., 2004) versus anxiety-dominant (Cameron et al., 2004) patterns of neuroendocrine functioning.

Evans et al. (2008) examined cortisol levels in a sample of pregnant women, both at baseline in the laboratory and in response to a standardized stressor. Participants were diagnosed with a depressive disorder alone (MDD or dysthymia), an anxiety disorder alone (any anxiety disorder except PTSD), currently co-occurring depressive and anxiety disorders (MDD or dysthymia, and any anxiety disorder except PTSD), or no diagnosis. Similar to the findings of Young et al. (2004), the participants with co-occurring depressive and anxiety disorders had significantly higher cortisol levels than did controls at all assessment time points; the groups with a depressive disorder alone and an anxiety disorder alone did not differ from controls. Again, these findings suggest a distinctive profile of cortisol functioning in co-occurrence, particularly in response to laboratory stressors.

In the one study that assessed diurnal cortisol production, Veen et al. (2011) included participants with MDD alone, an anxiety disorder alone (primarily PD, SAD, or PTSD), and co-occurring MDD-anxiety disorder (primarily PD, SAD, or PTSD). Compared to non-psychiatric controls, participants with MDD alone exhibited higher cortisol levels from the afternoon through evening; participants with both an anxiety disorder alone and co-occurring MDD-anxiety disorder did not differ from controls. These results suggest that the diurnal cortisol profile of anxiety disorders dominates or overshadows the influence of MDD, such that persons with co-occurring MDD-anxiety disorder appear most similar in functioning to those with an anxiety disorder alone. As a limitation of this study, however, the authors did not directly compare the three clinical groups with respect to their levels of cortisol production. Collectively, the findings for neuroendocrine functioning demonstrate that there are diverse profiles for co-occurrence across a range of different paradigms and measures. Despite the diversity of findings, the most consistent finding suggests that individuals with co-occurring anxiety and depression manifest a distinct neuroendocrine profile.

2.2. Neural functioning

The majority of studies in this area have focused on delineating the neurobiology of MDD alone, GAD alone, and co-occurring MDD-GAD, arguably the foci of the greatest intensity of debate with respect to nosology (Andrews et al., 2010; Hettema, 2008; Mennin et al., 2008). In a functional magnetic resonance imaging (fMRI) study, Etkin and Schatzberg (2011) examined neural responses during the regulation of emotional conflict in participants diagnosed with MDD alone, GAD alone, and co-occurring MDD-GAD relative to control participants. Whereas all three clinical groups demonstrated shared impairments in activation and connectivity of the ventral anterior cingulate cortex (ACC) and amygdala during the regulation of emotional conflict, only the group with MDD alone was able to compensate for this deficit through activation of the left and right anterior dorsolateral pre-frontal cortices (DLPFCs); the groups with GAD alone and MDD-GAD did not. This latter finding suggests that the neurobiological profile of GAD dominated or overshadowed the influence of co-occurring MDD such that persons with co-occurring MDD-GAD were most similar to those with GAD alone (i.e., a GAD-dominant profile for co-occurrence). More recently, Oathes et al. (2015) used resting-state fMRI to examine low-frequency signal amplitude and functional connectivity in these diagnostic groups. The diagnosis of MDD exerted a main effect on reduced signal amplitude across a range of brain regions (DLPFC/ medial prefrontal cortex as well as limbic/paralimbic and cingulo-opercular regions), such that both MDD alone and co-occurring MDD-GAD were characterized by lower overall signal amplitude than were GAD and control participants. The diagnosis of GAD exerted an effect on reduced signal amplitude only in limbic/paralimbic regions. In addition, there was a main effect of MDD diagnosis on decreased subgenual ACC/ ventral striatum connectivity and increased amygdala-subcortical connectivity. Thus, the resting neural signature of MDD-GAD appeared to most closely resemble that of MDD alone (i.e., an MDD-dominant profile for co-occurrence). Weinberg et al. (2015) used event-related potential (ERP) data to assess error monitoring, operationalized using the error-related negativity (ERN), which is conceptualized to reflect activity in the dorsal ACC. These authors observed a larger ERN in participants with GAD alone than in controls, which was not present in participants with

either MDD alone or co-occurring MDD-GAD. Here again, the response profile that characterized MDD seemed to dominate or overshadow co-occurring GAD.

Researchers have also examined patterns of neural activation in individuals diagnosed with MDD alone, SAD alone, and with co-occurring MDD-SAD. Waugh et al. (2012) assessed neural activations in response to a social stressor in participants diagnosed with MDD, SAD, and co-occurring MDD-SAD. Relative to levels of activation in a non-psychiatric control group, co-occurrence was characterized by activation in the medial frontal cortex similar to that exhibited in MDD alone, by activation in the occipital cortex and insula similar to that exhibited in SAD alone, and by intermediate activation in the dorsal ACC and posterior cingulate cortex that was between the levels of activation exhibited in MDD alone and in SAD alone. Thus, depending on the specific brain regions examined, co-occurrence was alternately characterized by activation patterns similar to those exhibited in MDD alone and in SAD alone (i.e., an additive profile), as well as intermediate activation between the levels exhibited in either disorder alone (i.e., an average profile). In this same sample of participants, Hamilton et al. (2015) reported even further diverse patterns for co-occurrence as participants listened to a series of statements delivering criticism and praise in the scanner. Depending on the specific neural metric, co-occurring MDD-SAD was alternately characterized by additive, distinctive, and shared profiles of activation.

Specifically, relative to controls, co-occurrence involved reduced activation to praise across a distributed cortisol network parallel to that in MDD alone, anomalous activation to criticism in the anterior insula and regions within default-mode network (DMN; Greicius et al., 2003) parallel to that in SAD alone (i.e., an additive profile), and a distinctive pattern of activation to praise in the dorsal ACC that was not shown in either disorder alone (i.e., a distinctive profile). All three clinical groups shared a profile of elevated response to criticism in the DLPFC (i.e., a shared profile). Thus, in the context of multivariate neuroimaging data, findings for co-occurring MDD-SAD appear particularly complex.

Studies of samples with other depressive and/or anxiety disorders have yielded equally complex findings. Shankman et al. (2013) recruited participants with MDD alone, PD alone, and co-occurring MDD-PD. Participants with both MDD and MDD-PD exhibited reductions in frontal electroencephalographic (EEG) asymmetry during reward anticipation, compared to non-psychiatric controls. In contrast, during threat anticipation, participants with both PD and MDD-PD exhibited elevated startle responses. Thus, depending on one's perspective, these results indicate that co-occurrence entails dominant effects of single disorders in specific domains of functioning (MDD dominance on the reward task and PD dominance on the threat task) or, conversely, an overall additive profile of the two disorders across the two domains. Finally, Bruder et al. (2002) examined ERPs during tonal and phonetic auditory oddball tasks in participants diagnosed with a depressive disorder alone (MDD or dysthymia), an anxiety disorder alone (GAD, SAD, PD, or Obsessive-Compulsive Disorder [OCD]), and co-occurring depressive-anxiety disorder (same diagnostic criteria as for the pure groups). The early component of the P3 potential, which reflects an orienting or alerting response, was reduced both in participants with a depressive disorder alone and in participants with co-occurring depressive-anxiety disorder relative to controls; however, the late component of the P3, which reflects cognitive effort, was largest in participants with co-

occurring depressive-anxiety disorder relative to those with either type of disorder alone. Finally, the level of task-dependent hemispheric asymmetry that was shown in co-occurrence was in between the levels of asymmetry that were shown in either type of disorder alone. Thus, across the various ERP metrics, co-occurrence was characterized by depression-dominant, additive, and average response profiles. As is clear both within and across all of these brain-based studies of co-occurring depression and anxiety, findings reflect highly variable patterns for co-occurrence in relation to those for pure disorders, paralleling the diverse findings for neuroendocrine functioning.

2.3. Autonomic functioning

Two studies have compared autonomic nervous system functioning across MDD alone, GAD alone, and co-occurring MDD-GAD. Chang et al. (2013) focused on resting respiratory sinus arrhythmia (RSA), which reflects largely parasympathetic control over heart rate. These authors found that resting RSA was significantly reduced in both GAD alone and MDD-GAD relative to controls, and was even lower in MDD-GAD than in GAD alone, thus demonstrating a distinctively more severe autonomic profile for co-occurrence of MDD-GAD. In a more recent study of RSA responses to a social stressor, Kircanski et al. (2016) documented that, compared to non-psychiatric controls, participants with MDD alone, GAD alone, and co-occurring MDD-GAD all exhibited blunted patterns of RSA responsivity during and following the stressor. In contrast to the findings on resting RSA of Chang et al. (2013), however, levels of RSA both at baseline and in response to the stressor did not differ among these three clinical groups, indicating a shared profile of parasympathetic functioning.

2.4. Summary of categorical research

Taken together for the first time, the current evidence highlights the complexity of understanding co-occurrence from a diagnostic perspective. The findings reviewed above are highly varied in providing support for all of the types of conceptual profiles that may be observed in co-occurrence, including additive, average, single-disorder dominant, distinctive, and shared profiles, without a unifying theory emerging for specific units of analysis or domains of functioning. One possible trend for co-occurrence is the tendency for MDD-related responding to predominate in paradigms or measures that index reward constructs, and for anxiety-related responding to predominate in threat-based assessments (Hamilton et al., 2015; Shankman et al., 2013), but even here the evidence is equivocal (Evans et al., 2008; Kircanski et al., 2016; Waugh et al., 2012; Weinberg et al., 2015; Young et al., 2004). Furthermore, the degree of variability in findings for specific diagnostic combinations (e.g., MDD and GAD), and even for single samples, is similar to the degree of variability that is shown across studies with more heterogeneous groups within a single disorder (e.g., any depressive disorder and any anxiety disorder). Therefore, the complexity in findings does not appear attributable to the diversity in the recruitment criteria or diagnostic composition of these studies. Whereas differences in sample and effect sizes across studies may influence their relative statistical power to detect differences among clinical groups (e.g., finding a shared versus additive profile for co-occurrence), issues of sample size or power cannot explain the host of entirely opposing results across studies (e.g., finding a depression-dominant versus anxiety-dominant profile for co-occurrence).

Instead, these inconsistent results may be due, in part, to the heterogeneity within current *DSM* categories or to logical fallacies inherent in any categorical conceptualization of psychobiological functioning. Indeed, even participants in 'pure' diagnostic groups are likely to exhibit subclinical symptoms of the other diagnostic category (Ionescu et al., 2013; Rodríguez et al., 2012), thereby blurring boundaries among groups. Extant data also strongly support two distinct types of anxiety symptoms – anxious arousal (physiological symptoms) and anxious apprehension (worry) –which have differing psychobiological substrates that are confounded when investigators treat anxiety or anxiety disorders as a unitary construct (e.g., Bijsterbosch et al., 2014; Heller et al., 1997; Nitschke et al., 2001; Nitschke et al., 1999; Watson, 2005). In addition, biases are inherent when the features of disorders are defined through comparisons to the functioning of (often lifetime-) diagnosis-free control participants. As is well documented, studying only individuals who lie at the extremes of symptom dimensions may lead researchers to misconstrue the true nature of population-level effects and reduce statistical power relative to a more dimensional recruitment and measurement strategy (MacCallum et al., 2002; Preacher et al., 2005). Finally, from a logistical research perspective, it seems a relatively unwieldy and inefficient prospect to compare the large number of possible combinations of co-occurring versus non-co-occurring disorders in each of the many important domains of functioning.

3. Toward a dimensional model of co-occurrence

Increasingly, the scientific community is recognizing that diagnostic categories are not the optimal units on which to classify and compare individuals for the purposes of understanding pathophysiology and ultimately improving therapeutics. Instead, investigators both within and outside of the domains of depression and anxiety are advocating taking a dimensional approach to psychopathology in which individuals' functioning is characterized along continuous measures that operationalize core psychobiological constructs (Goldberg, 2000; Helzer et al., 2006; Insel et al., 2010; Levine et al., 2001; Widiger and Clark, 2000; Widiger and Samuel, 2005). With respect to the particular issue of comorbidity, theorists have argued cogently for a dimensional framework that captures the shared features of depression and anxiety that might be targeted in unified or transdiagnostic, as opposed to diagnosis-specific, treatment strategies (Barlow et al., 2004; Pollack, 2005). Although this approach represents a significant departure from a disorder-specific treatment perspective, however, even a fully transdiagnostic model does not account for the interactions that can occur between depressive and anxiety symptoms and that may be most relevant to understanding the functioning of individuals who have co-occurring high levels of both types of symptoms (Dillon et al., 2014). Broadly, the concept of interactions reflects the formulation that people's level of functioning along one dimension can dynamically influence their functioning along another dimension. For instance, an individual's current level of depressive anhedonia may moderate the observed psychobiological correlates of anxious arousal. Thus, quantifying such interactions may help to reduce the problematic heterogeneity of findings that are obtained when studying the features of only one symptom dimension (or diagnosis [Insel, 2013]) in isolation.

In this context, we advocate adopting a multi-dimensional assessment strategy for investigating the nature of co-occurrence, in which individuals' functioning along both

depression- and anxiety-relevant continuous measures is quantified simultaneously in order to efficiently capture the dimensions' *unique, shared, and interactive* features. Fig. 2 presents this alternative dimensional approach to studying depression and anxiety, which provides information about a wide range of presentations, from relatively pure to highly comorbid symptoms. As shown, unique features reflect cases in which individuals' levels of depressive and anxiety symptoms are associated with different psychobiological correlates (e.g., levels of depressive symptoms are related to greater regional neural activation, whereas levels of anxiety symptoms are not). Shared features reflect cases in which individuals' levels of depressive and anxiety symptoms are associated with similar psychobiological correlates (e.g., levels of both depressive symptoms and anxiety symptoms are related to greater regional neural activation). Finally, interactive features refer to cases in which individuals' co-occurring levels of depressive and anxiety symptoms interact statistically, or moderate each other, with respect to psychobiological functioning (e.g., a high level of anxiety symptoms lessens the relation between a high level of depressive symptoms and greater neural activation).

To date, no studies have examined the independent and interactive relations of depressive and anxiety symptom dimensions to neuroendocrine or autonomic functioning. Thus, below, we focus our review on the nascent research on neural functioning.

3.1. Neural functioning

Four studies have tested the dimensional associations of depression, anxiety, and their interaction with brain-based functioning, the first three of which were conducted by Heller, Miller, and their colleagues. Keller et al. (2000) examined perceptual asymmetry on a face processing task as an index of regional brain activity. In two separate samples, participants were recruited on the basis of meeting criteria for MDD or no history of a psychiatric disorder (Study 1), or on the basis of scores on self-report measures of anxious arousal, anxious apprehension, and anhedonic depression (Study 2). In both samples, levels of depressive symptoms (Beck Depression Inventory [BDI] scores; Beck and Steer, 1987), levels of trait anxiety (State-Trait Anxiety Inventory-Trait scale [STAI-T] scores; Spielberger et al., 1983), and their interaction were tested simultaneously in relation to perceptual asymmetry scores. These investigators found that the depressive and anxiety dimensions were associated with unique patterns of hemispheric asymmetry, characterized by smaller versus larger right-hemisphere biases, respectively. Furthermore, the interaction between depressive symptoms and trait anxiety significantly predicted hemispheric asymmetry: when levels of both dimensions were high, a relatively larger right-hemisphere bias was evident. Given that the direction of the interaction paralleled the direction that was found for trait anxiety, this indicates a buffering effect of anxiety on depression-associated hemispheric biases. Keller et al. interpreted these results to suggest that a component of anxiety that is not shared with depression, perhaps high arousal, might drive this relative increase in right-hemispheric asymmetry. It is important to note that these findings were consistent across the two samples despite the differences in their recruitment criteria.

Engels et al. (2010) examined patterns of neural activation during an fMRI task that required top-down attentional control in the presence of negative distractors. Ninety-one participants

were recruited on the basis of self-reported anhedonic depression, anxious arousal (Mood and Anxiety Symptom Questionnaire [MASQ] subscale scores; Watson et al., 1995a, 1995b), and anxious apprehension (Penn State Worry Questionnaire [PSWQ] scores; Meyer et al., 1990); consequently, a range of symptom levels and their combination were represented in the sample. Most notably, Engels et al. found a series of significant interactions between anhedonic depression and anxious arousal. Higher levels of anhedonic depression were associated most strongly with right frontal lateralization in the DLPFC and reduced activation in the right inferior frontal gyrus when co-occurring levels of anxious arousal were also high. These authors concluded that co-occurring high levels of depression and anxious arousal are associated with particularly severe impairments in top-down attentional control in the presence of salient negative material. In addition, patterns of neural activity were shown to diverge in relation to anxious arousal versus anxious apprehension; high levels of anxious apprehension were generally not associated with the same deleterious effects that were found for high levels of anxious arousal.

More recently, Warren et al. (2013) examined the neural correlates of inhibition, including self-reported inhibition and pre-potent response inhibition assessed using a Stroop paradigm in the scanner. Participants completed the same measures of anhedonic depression, anxious arousal, and anxious apprehension that were utilized in Engels et al. (2010) and, again, participants represented a range of symptom levels and their combination. Contrary to expectations, there were few significant interactive effects of depression and anxiety on activity in brain regions that were associated with self-reported inhibition. However, co-occurring levels of anhedonic depression and levels of anxious apprehension interacted to predict neural correlates of inhibitory control: higher levels of depression were associated with lower levels of activation in the right frontal pole when anxious apprehension was low, but not when anxious apprehension was high. The authors postulated that co-occurring anxious apprehension serves to benefit inhibitory performance in individuals with high levels of depressive symptoms. Clinically, this suggests that worry is actually adaptive for individuals with high depressive symptoms when they are attempting to inhibit prepotent responses.

Finally, Dotson et al. (2014) examined levels of self-reported depressive symptoms (Center for Epidemiological Studies-Depression [CES-D] scores; Radloff, 1977), levels of trait anxiety (STAI-T scores), and their interaction as predictors of neural activation when attempting to control information in working memory. Participants were selected from a general community sample with an age range into older adulthood. Higher levels of depressive symptoms were associated with poorer executive functioning and reduced activity in the superior frontal gyrus when controlling material in working memory in participants with lower levels of trait anxiety. Higher co-occurring levels of trait anxiety buffered against these depression-related impairments. Given that the construct of trait anxiety is distinct from both anxious arousal and anxious apprehension, it is currently unclear whether these findings are consistent with or potentially contradictory to the earlier studies of executive functioning (Engels et al., 2010; Warren et al., 2013). However, across these studies, a general trend is that depressive and anxiety symptom dimensions are associated with distinct patterns of neural functioning, which interact with one another in relation to the neurobiological measures.

Clearly, further dimensionally-focused research is needed to provide greater insight into the brain-based dynamics that characterize co-occurrence. In addition, it will be critical in future work to examine different ways of operationalizing dimensional co-occurrence. The reviewed studies operationalized co-occurrence as concurrent high levels of two symptom dimensions, relative to the mean levels of symptoms within the samples, often utilizing values that are one standard deviation above the respective means in order to illustrate the findings. Future investigations, however, may utilize additional information such as level of functional impairment in order to further characterize the clinical significance of symptoms.

4. Illustration of multi-dimensional research approach

Building on this emerging area of research, in this section we utilize a new dataset to examine the unique, shared, and interactive features of depression and anxiety in relation to diurnal cortisol secretion. In order to directly compare the proposed dimensional approach to a traditional categorical perspective, we recruited participants on the basis of diagnoses of MDD, GAD, and co-occurring MDD-GAD, in addition to non-psychiatric control participants, and we assessed depressive symptoms and symptoms of anxious arousal and apprehension along a continuum. The participants whose data are analyzed and reported here represent a subset of the sample reported in Kircanski et al. (2016), for which we documented a shared profile of functioning with respect to parasympathetic responses to stress. In the current analysis, we focused on diurnal cortisol production. Cortisol secretion follows a strong circadian pattern, with the highest levels secreted approximately 30–40 min after awakening (the cortisol awakening response [CAR]) and dropping to low levels thereafter until late evening (Kirschbaum and Hellhammer, 1994). Individual differences in patterns of diurnal cortisol production have been implicated in the etiology of both depression and anxiety (Herbert, 2013; Stetler and Miller, 2005; Vreeburg et al., 2009, 2010), and are featured prominently in the NIMH RDoC. The RDoC initiative incorporates the CAR as a paradigm to assess the construct of arousal within the Arousal and Regulatory System. In addition, neuroendocrine functioning is listed as a unit of analysis for several constructs within the RDoC Negative Valence System, underscoring the potential links of diurnal cortisol to negative emotional systems and symptoms.

4.1. Participants

Fifty-eight adult women between the ages of 18 and 50 years were recruited through online advertisements and local psychiatric clinics, and were screened for inclusion/exclusion criteria through a telephone interview. Exclusion criteria were: *DSM-IV* bipolar I or II; alcohol or substance abuse in the past six months; psychotic symptoms; learning disabilities; and history of severe head trauma.

4.2. Diagnostic groups

Individuals who were identified as likely to meet inclusion criteria for current MDD, GAD, or co-occurring MDD-GAD participated in a laboratory evaluation using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I) (First et al., 1996), administered by trained interviewers. The sample was designed to include a mixture of diagnostic presentations: MDD alone (n=11); GAD alone (n=13); currently co-occurring MDD-GAD

(n=18); and no current or lifetime Axis I disorder (n=16). We required that participants in the MDD-alone and GAD-alone groups did not meet criteria for co-occurrence within the past 24 months. For the co-occurring MDD-GAD group, we did not apply the *DSM-IV* hierarchical exclusion criterion (reviewed in Andrews et al., 2010). Diagnostic inter-rater reliability in the present sample was excellent for both MDD (k=1.00) and GAD (k=0.87). Table 1 presents the demographic and clinical characteristics for the diagnostic groups.

4.3. Symptom dimensions

Participants' levels on the symptom dimensions were assessed using three continuous measures; data were not available for six participants due to an error in electronic questionnaire administration.

4.3.1. Depressive symptoms—The Center for Epidemiological Studies-Depression (CES-D; Radloff, 1977) is a 20-item self-report measure that assesses core depressive symptoms experienced during the past week with well-established validity and reliability. Developed for use with the general population, the CES-D has been demonstrated to have good sensitivity across a range of levels of depressive symptoms and, thus, is advantageous for dimensional analyses in a mixed diagnostic sample.

4.3.2. Anxious arousal—The Beck Anxiety Inventory (BAI; Beck et al., 1988) is a 21-item self-report measure that emphasizes physiological symptoms of anxiety with high validity and reliability. Importantly, the BAI measures and isolates the construct of anxious arousal, which we posited would be particularly relevant to diurnal cortisol as an index of the Arousal and Regulatory System and thus was the focus of our analyses. In addition, the BAI was designed to minimize overlap with depressive symptoms and, therefore, is useful in analyses that examine the effects of these two symptom dimensions.

4.3.3. Anxious apprehension—The Generalized Anxiety Disorder Questionnaire-IV (GAD-Q-IV; Newman et al., 2002) is a 9-item self-report measure that assesses worry and associated symptoms of GAD and has demonstrated good validity and reliability. Although our primary analyses focused on the BAI, we used the GAD-Q-IV in order to compare findings for anxious arousal versus anxious apprehension. BAI and GAD-Q-IV scores were correlated with one another in the sample, r=.76, $p < .001$.

4.4. Diurnal cortisol assessment

Salivary cortisol was collected within two weeks of the diagnostic session using salivette kits (Sarstedt, Germany). Participants completed the protocol over two consecutive days and were instructed to provide four measurements per day: immediately upon awakening; 30 min post-awakening; at approximately 3 pm in the mid-afternoon; and 30 min before bedtime. A minimum of 0.2 ml of liquid saliva was absorbed into a small cotton roll and expressed through a plastic tube into a sterile vial. Participants were instructed to place the salivettes in a freezer immediately after sampling until all measurements were completed. In cases in which participants were outside of the home (e.g., at work), they were instructed to, whenever possible, identify a refrigerator or freezer at that location for temporary storage. Participants returned all samples to the laboratory. Quality assurance included review of the

samples and reported days/times of completion by research personnel. Samples were transferred to a −20º F freezer in the Stanford University General Clinical Research Center until radioimmunoassay. Samples were assayed together to control for inter-assay error, and control samples were included to evaluate variability. Cortisol levels were assayed using luminescence immunoassay reagents through a commercial kit from Immuno-Biological Laboratories Inc. (Hamburg, Germany). The assay sensitivity was set at 0.015 mg/dl.

4.5. Statistical analyses

Consistent with previous research (Chen et al., 2009), cortisol values were winsorized to 2 *SD* from the mean (Tukey, 1977). As expected, day of collection did not explain a significant proportion of variance in the cortisol measures (ICCs < .10; Lee, 2000); therefore, cortisol values and the corresponding times of day at each sampling point were averaged across the two days. To examine the relations of depression and anxiety diagnoses and symptom dimensions to the diurnal cortisol measures while accounting for the nested structure of the data, we conducted multilevel modeling using HLM software, Version 6.08 (Raudenbush et al., 2004). Within-person diurnal fluctuations in cortisol levels were quantified at Level 1 using a two-rate piecewise linear growth model (Raudenbush and Bryk, 2002) to simultaneously account for the diurnal fluctuations of the CAR and the afternoon decline in cortisol:

$$\text{Cortisol}=\pi_{0j}(\text{CAR})+\pi_{1j}(\text{peak})+\pi_{2j}(\text{afternoon decline})+e_{ij}$$

in which $\boldsymbol{\pi}_{0j}$ denotes the slope of cortisol as a function of the amount of time (in hours) between the awakening and post-awakening measurements for participant j, $\boldsymbol{\pi}_{1j}$ denotes the peak (post-awakening) cortisol level for participant j, and $\boldsymbol{\pi}_{2j}$ denotes the slope of cortisol as a function of the amount of time (in hours) between the post-awakening and bedtime measurements for participant j. Between-person differences in these cortisol measures were quantified at Level 2, using either a categorical model or a dimensional model, as described below.

5. Results

5.1. Categorical approach

At Level 2, we examined differences among the four diagnostic groups in the CAR, peak cortisol, and afternoon decline in cortisol. Groups were coded using a set of dummy variables (MDD, GAD, MDD-GAD, CTL) through which participants' membership in each group was designated (0=participant is not in group; 1=participant is in group). An initial analysis of potential covariates in our dataset (age, race [Non-Hispanic White], body mass index [BMI], use of psychotropic medication, self-reported sleep quality, self-reported exercise) indicated that selected cortisol measures were associated with only age and BMI, which were therefore included as control variables, centered at the grand mean, in all analyses. First, we compared each clinical group to the CTL group:

$$\text{CAR: } \pi_{0j}=\beta_{00}+\beta_{01}(\text{MDD})+\beta_{02}(\text{GAD})+\beta_{03}(\text{MDD}-\text{GAD})+\beta_{04}(\text{age})+\beta_{05}(\text{BMI})+r_0$$
$$\text{Peak: } \pi_{1j}=\beta_{10}+\beta_{11}(\text{MDD})+\beta_{12}(\text{GAD})+\beta_{13}(\text{MDD}-\text{GAD})+\beta_{14}(\text{age})+\beta_{15}(\text{BMI})+r_1$$
$$\text{Afternoon decline: } \pi_{2j}=\beta_{20}+\beta_{21}(\text{MDD})+\beta_{22}(\text{GAD})+\beta_{23}(\text{MDD}-\text{GAD})+\beta_{24}(\text{age})+\beta_{25}(\text{BMI})+r_2$$

β_{00} denotes the mean level of the CAR in the CTL group at the mean of all covariates, and β_{01} denotes the difference in mean level of the CAR between the CTL group and the MDD group; this same system of denotation holds for β_{02} to β_{23}.

Table 2 (left portion) presents the coefficient estimates and significance tests for the categorical models. One group difference was marginally significant: the MDD group exhibited marginally lower peak cortisol than did the CTL group, p=.055. The MDD group did not differ significantly from the CTL group in the CAR, p=.589, or afternoon decline in cortisol, p=.143; further, the GAD and MDD-GAD groups did not differ significantly from the CTL group in the CAR (ps>.679), peak cortisol (ps>.285), or afternoon decline in cortisol (ps>.351).

We also compared cortisol functioning among the three clinical groups by changing the reference group in the Level 2 models. There were no significant differences among the clinical groups in the CAR (ps > .737), peak cortisol (ps > .275), or afternoon decline (ps > . 247).

5.2. Dimensional approach

Next, we examined the main and interactive effects of continuously-assessed depressive and anxiety symptoms in relation to the CAR, peak cortisol, and afternoon decline in cortisol by specifying a model with the continuous predictors at Level 2. We included the same covariates as we did in the categorical models; we also covaried the CTL group at Level 2 in attempt to reduce artificial inflation of the dimensional associations with cortisol on the basis of clinical versus control group status (see Oathes et al., 2015; Veen et al., 2011). The symptom dimension variables were transformed to z-scores in order to compare the reported coefficient estimates with regard to size.

5.2.1. Depressive symptoms and anxious arousal—As the primary dimensional analysis, we examined the main and interactive effects of CES-D and BAI scores:

$$\text{CAR: } \pi_{0j}=\beta_{00}+\beta_{01}(\text{CES}-D)+\beta_{02}(\text{BAI})+\beta_{03}(\text{CES}-D\times\text{BAI})+\beta_{04}(\text{age})+\beta_{05}(\text{BMI})+\beta_{06}(\text{CTL})+r_0$$
$$\text{Peak: } \pi_{1j}=\beta_{10}+\beta_{11}(\text{CES}-D)+\beta_{12}(\text{BAI})+\beta_{13}(\text{CES}-D\times\text{BAI})+\beta_{14}(\text{age})+\beta_{15}(\text{BMI})+\beta_{16}(\text{CTL})+r_1$$
$$\text{Afternoon decline: } \pi_{2j}=\beta_{20}+\beta_{21}(\text{CES}-D)+\beta_{22}(\text{BAI})+\beta_{23}(\text{CES}-\text{D}\times\text{BAI})+\beta_{24}(\text{age})+\beta_{25}(\text{BMI})+\beta_{26}(\text{CTL})+r_2$$

β_{00} denotes the mean level of the CAR at the mean of all variables, and β_{01} denotes the relation between the mean level of the CAR and CES-D score; this same system of denotation holds for β_{02} to β_{23}.

Table 2 (right portion) presents the coefficient estimates and significance tests for the dimensional models. There were several significant unique and interactive relations of CES-D and BAI scores to the cortisol measures. First, higher BAI scores were associated with a

steeper CAR, p=.042; this was qualified by an interactive effect of CES-D and BAI scores on the CAR, p=.043. Second, higher BAI scores were associated with higher peak cortisol, p=.039; again, this was qualified by an interactive effect of CES-D and BAI scores on peak cortisol, p=.001. Third, higher CES-D scores were associated with a flattened afternoon decline in cortisol, p=.043, whereas higher BAI scores were associated with a marginally steeper afternoon decline in cortisol, p=.063. These unique effects were qualified by an interactive effect of CES-D and BAI scores on the afternoon decline in cortisol, p=.005.

Fig. 3 depicts the nature of these interactive effects, which we tested formally using simple slope and Region of Significance (RoS) analyses (Preacher et al., 2006). With respect to the CAR and peak cortisol, higher BAI scores were associated with a steeper CAR and higher peak cortisol when CES-D scores were low (M−1 SD; ps < .029) or intermediate (M; ps < .042). However, BAI scores were not significantly associated with the CAR or peak cortisol when CES-D scores were high (M+1 SD; ps>.430). In RoS analyses, higher BAI scores were associated with a steeper CAR and higher peak cortisol when CES-D z-scores were less than 0.08 (raw scores < 21.35). Stated differently, for participants with higher BAI scores, lower CES-D scores were associated with a relatively steeper CAR and higher peak cortisol, whereas higher CES-D scores were associated with a relatively blunted CAR and lower peak cortisol. Finally, with respect to afternoon decline in cortisol, higher BAI scores were associated with a steeper afternoon decline when CES-D scores were low (p=.016) or intermediate (p=.063; marginal); however, BAI scores were not significantly associated with the afternoon decline when CES-D scores were high (p=.826). In RoS analyses, BAI scores were associated with a steeper afternoon decline when CES-D z-scores were less than −0.11 (raw scores < 18.45). Thus, for participants with higher BAI scores, lower CES-D scores were associated with a relatively steeper afternoon decline, whereas higher CES-D scores were associated with a relatively flattened afternoon decline in cortisol.

5.2.2. Depressive symptoms and anxious apprehension—In a parallel manner, we examined the main and interactive effects of CES-D and GAD-Q-IV scores. As in the previous model, higher CES-D scores were associated with a flattened afternoon decline in cortisol, p=.012. No other main or interactive effects were significant with respect to the CAR (ps>.207), peak cortisol (ps>.322), or afternoon decline in cortisol (ps > .346).

6. Discussion of illustrative data analysis

In brief, the results of our example data analysis both support and advance key themes in the growing literature on the co-occurrence of depression and anxiety. First, we found that levels of depressive symptoms and anxious arousal, assessed on a continuum, interacted with each other in their relations to diurnal cortisol secretion. Most notably, among participants with higher levels of anxious arousal, differing levels of depressive symptom severity were related to significantly varying diurnal profiles across the CAR, peak cortisol, and afternoon decline in cortisol. Specifically, lower levels of depressive symptoms were associated with a more pronounced (i.e., steeper) diurnal profile, whereas higher levels of depressive symptoms, as in co-occurrence, were associated with a more blunted (i.e., flattened) diurnal profile. Viewed another way, at higher levels of depressive symptoms, the anxiety symptom dimension was associated with fewer individual differences in diurnal cortisol production

rates. These interactions may help to explain the heterogeneity of previous findings concerning cortisol functioning when depression and anxiety diagnoses were studied in isolation (Herbert, 2013; Knorr et al., 2010).

Second, relative to a traditional categorical approach, the dimensional approach to symptom assessment and analysis yielded much richer and more precise information about the ways in which varying symptom presentations are related to individual differences in diurnal cortisol production. Although similar comparisons between categorical and dimensional models have been made by other investigators, they have not reported dimensional interactions (Oathes et al., 2015; Veen et al., 2011). Third, the present results both support and extend the neurobiological distinction that has been established between the anxious arousal and anxious apprehension systems (Heller et al., 1997; Nitschke et al., 1999; Watson, 2005): we found these two symptom dimensions to have divergent relations to diurnal cortisol secretion. In the context of the RDoC initiative, these findings indicate a consistent relation between the anxious arousal, but not the anxious apprehension, symptom dimension and the RDoC construct of arousal as measured with diurnal cortisol.

6.1. Limitations

There are also several limitations of these illustrative data that should be noted in considering the development of dimensional research paradigms. The first set of limitations concerns aspects of our sample: we examined a small sample of women only, we recruited participants on the basis of a specific combination of depressive and anxiety disorders, and participants were mixed with respect to psychotropic medication use. The current analyses were based, in large part, on our goal of directly comparing diagnostic and dimensional models as a complement to our review of previous studies. This approach, however, resulted in a less optimal distribution of symptom severity than has been proposed in previous methodological research (Beuke et al., 2003; Ingram and Hamilton, 1999), which should be considered in recruiting and selecting participants in future studies. In addition, it is likely that the strongest comparison of categorical versus dimensional approaches will involve larger sample sizes. Further, larger samples will allow for the testing of possible subtle, non-linear interactions among dimensions, rather than only linear specifications as presented here. Second, we focused our assessment on canonical depressive and anxiety symptom dimensions. Further research may also integrate emerging transdiagnostic symptoms such as perseverative thinking (Ehring and Watkins, 2008) and levels of general distress, theorized to be shared across depression and anxiety disorders (Clark and Watson, 1991). In such work, it may be valuable to examine the correlates of both shared and unshared variance across dimensions (e.g., the correlates of anxious arousal that are shared versus not shared with general distress). Third, our review and data analysis focused on adult samples. It will be critical in future research to incorporate a longitudinal perspective on the early development of these symptoms and their potential interactive effects. Latent curve models may be particularly useful in estimating interactions among symptoms in their developmental trajectories. In this regard, Silk et al. (2012) and Dillon et al. (2014) recently provided evidence concerning the causal influences of anxiety-relevant threats on depression-relevant reward processes.

7. Summary and call for future research

In sum, it is indisputable that co-occurring depression and anxiety must be directly studied and treated; precisely how to do so remains a challenge. In this article, we have brought together the direct evidence for co-occurrence, from both categorical and dimensional investigations and across neural, neuroendocrine, and autonomic levels of analysis. Based on all of this evidence, we propose that a dimensional research model confers numerous conceptual and practical advantages. We argue that it will be most efficient in identifying psychobiological markers of psycho-pathologies, which will ultimately guide the development and selection of the most effective treatments for a wide range of individual patient presentations. Even within our relatively small sample, we observed significant interactive relations of depression and anxiety to neuroendocrine functioning that were not observed when using a categorical approach.

As we shift research lenses from a traditional focus on single disorders, to co-occurring diagnoses, to co-occurring symptom dimensions, the relations between psychopathology and psychobiology seem to become less static, instead leading to a more dynamic understanding of psychobiological systems. Importantly, an interactive dimensional model can be applied flexibly to other symptom dimensions that characterize other common forms of psychiatric comorbidity, examined in relation to a wide variety of psychobiological measures. In the not-too-distant future, it is also possible that the psychobiological measures themselves will become the predominant dimensions of focus, which are then examined in relation to novel clinical and functional end points.

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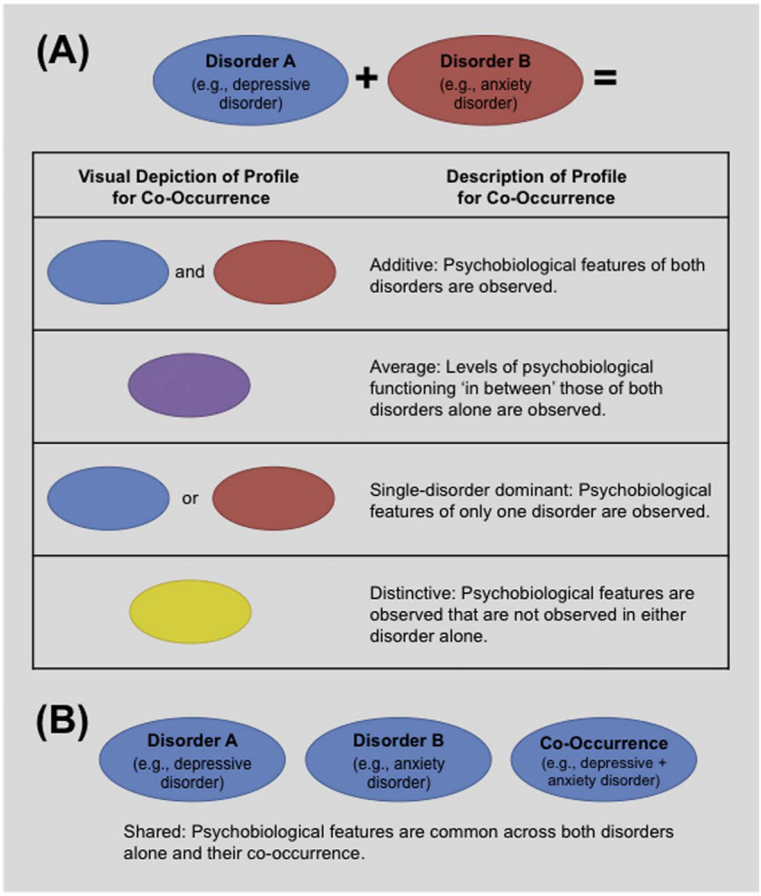

Fig. 1.

Examples of diverse psychobiological profiles that may be observed in individuals with two co-occurring disorders on the basis of the presumed features of each disorder alone. *Note.* Color denotation visually represents the profile of functioning observed in a given disorder (i.e., a disorder 'feature'), compared to the profile of functioning observed in a control group, for particular psychobiological measures of interest (e.g., cortisol awakening response [CAR] and afternoon decline in cortisol). (A) Different colors denoted for Disorder A and Disorder B indicate unique psychobiological features (e.g., a flattened CAR versus a steeper afternoon decline). The table illustrates the varied possible profiles of functioning that may be observed when the two disorders co-occur. (B) The same color denoted for Disorder A, Disorder B, and the two co-occurring disorders presents an alternative model of a shared profile of functioning for the measure of interest (e.g., a flattened CAR and steeper afternoon decline across all groups). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

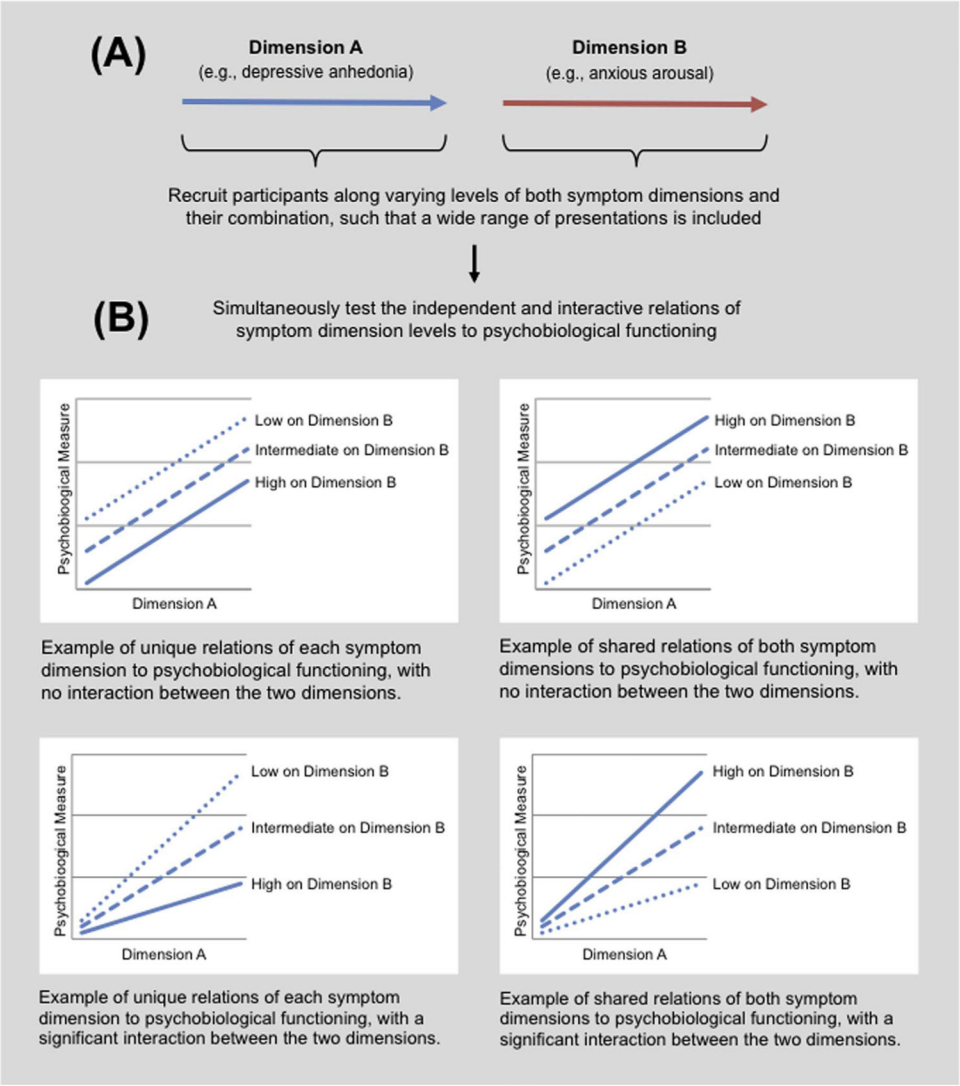

Fig. 2.

Research approach for investigating the unique, shared, and interactive relations of two symptom dimensions to psychobiological functioning. *Note.* (A) Specific recommendations for sample selection with respect to levels of both depressive and anxiety symptoms are provided in Beuke et al. (2003) and Ingram and Hamilton (1999) and illustrated in Oehlberg et al. (2012). (B) Graphs on the left illustrate a unique positive relation of scores on Dimension A, and a unique negative relation of scores on Dimension B, to levels of functioning along the psychobiological measure of interest. In the top left graph, parallel lines indicate that scores on the two dimensions do not interact in their relation to the psychobiological measure. In the bottom left graph, non-parallel lines indicate a significant interaction between scores on the two dimensions in their relation to the psychobiological measure. Graphs on the right illustrate a shared positive relation of scores on Dimension A and scores on Dimension B to levels of functioning along the psychobiological measure. In the top right graph, parallel lines indicate that scores on the two dimensions do not interact in their relation to the psychobiological measure. In the bottom right graph, non-parallel

lines indicate a significant interaction between scores on the two dimensions in their relation to the psychobiological measure.

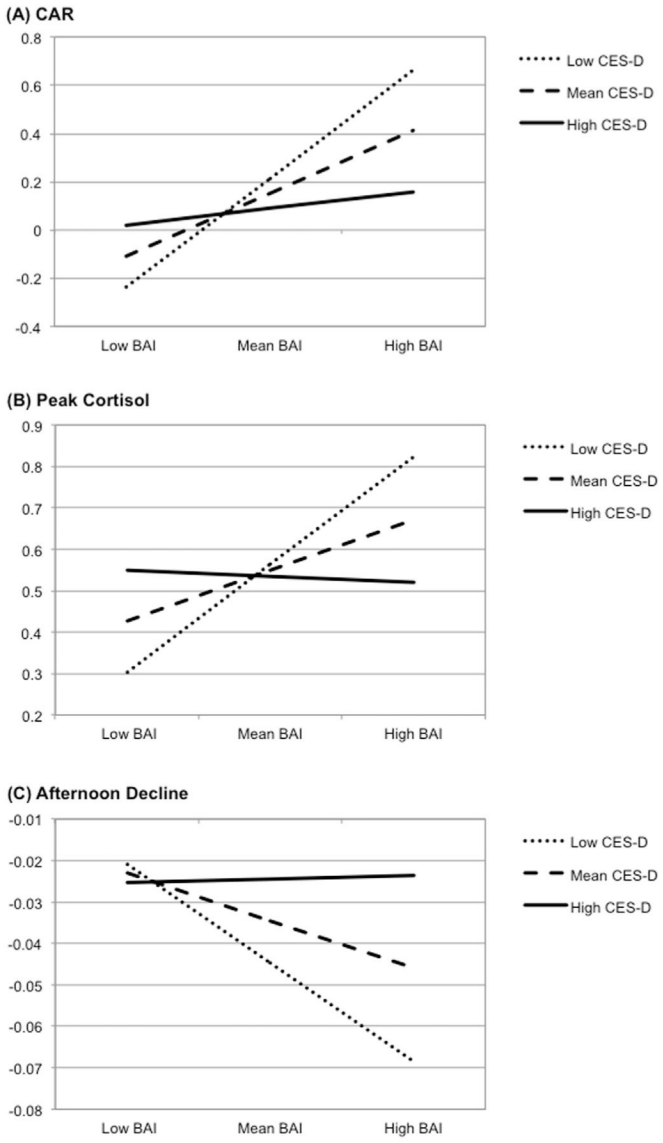

Fig. 3.

Interactive effects of depressive symptoms and anxious arousal on the cortisol awakening response (CAR), peak (post-awakening) cortisol, and afternoon decline in cortisol. *Note.* (A) Higher BAI scores associated with a steeper CAR, β=0.26, *p*=.042; qualified by an interactive effect of CES-D and BAI scores on the CAR, β= −0.19, *p*=.043. (B) Higher BAI scores associated with higher peak cortisol, β=0.12, *p*=.039; qualified by an interactive effect of CES-D and BAI scores on peak cortisol, β= −0.14, *p*=.001. (C) Higher CES-D scores associated with a flattened afternoon decline in cortisol, β=0.01, *p*=.043, and higher BAI scores associated with a marginally steeper afternoon decline in cortisol, β= −0.01, *p*=.063; qualified by an interactive effect of CES-D and BAI scores on the afternoon decline in cortisol, β=0.01, *p*=.005.

Table 1

Demographic and clinical characteristics of the diagnostic groups.

	MDD (*n*=11)	GAD (*n*=13)	MDD-GAD (*n*=18)	CTL (*n*=16)
	***M* (*SD*) or %**	***M* (*SD*) or %**	***M* (*SD*) or %**	***M* (*SD*) or %**
Age	34.82 (10.61)	31.38 (7.30)	36.00 (10.54)	35.88 (10.22)
Race/ethnicity *				
Non-Hispanic White	36.36%^{b}	61.54%^{a,b}	61.11%^{a,b}	80.00%^{a}
Hispanic	0.00%	15.38%	11.11%	0.00%
African-American	0.00%	0.00%	0.00%	13.33%
Asian-American	18.18%^{a,b}	23.08%^{b}	16.67%^{a,b}	0.00%^{a}
Mixed Race/Other	45.45%^{b}	0.00%^{a}	11.11%^{a}	6.67%^{a}
% college educated	54.55%	61.54%	66.67%	68.75%
% using psychotropic medication	45.45%^{b}	15.38%^{a,b}	27.78%^{b}	0.00%^{a}
SSRI	18.18%	0.00%	11.11%	0.00%
Atypical antidepressant	18.18%	0.00%	16.67%	0.00%
Benzodiazepine	0.00%	15.38%	16.67%	0.00%
Other	36.36%^{b}	7.69%^{a,b}	11.11%^{a,b}	0.00%^{a}
GAF	55.45 (5.39)^{c}	63.15 (5.38)^{b}	54.72 (5.76)^{c}	90.63 (6.46)^{a}
CES-D	30.64 (14.24)	18.08 (8.65)^{b}	30.67 (13.15)^{c}	3.27 (3.47)^{a}
	range: 8–46	range: 3–30	range: 12–53	range: 0–12
BAI	15.82 (11.63)^{b}	22.36 (8.96)^{b}	21.75 (9.96)^{b}	1.49 (1.65)^{a}
	range: 4–45	range: 10–37	range: 4–43	range: 0–4

Note. Abbreviations: BAI=Beck Anxiety Inventory; CES-D=Center for Epidemiological Studies-Depression; CTL=non-psychiatric control group; GAD=Generalized Anxiety Disorder; GAF=Global Axis of Functioning; *M*=mean; MDD=Major Depressive Disorder; *SD*=standard deviation; SSRI=selective serotonin reuptake inhibitor.

* Race/ethnicity data was missing for one participant.

^{a,b,c} Different superscripts within a row indicate significant differences between groups on the associated variable, $p<.05$.

Table 2

Results of primary categorical and dimensional hierarchical linear models of the CAR, peak (post-awakening) cortisol, and afternoon decline in cortisol.

Categorical Model[a]	**Coefficient**	***SE***	***t***	***p***	**Dimensional Model**[b]	**Coefficient**	***SE***	***t***	***p***
CAR (linear)	0.19	0.14	1.41	.166	*CAR (linear)*	0.15	0.09	1.62	.112
MDD	0.11	0.20	0.54	.589	CES-D	−0.06	0.11	−0.56	.580
GAD	0.08	0.18	0.42	.679	BAI	**0.26**	0.12	2.09	**.042**
MDD-GAD	0.04	0.19	0.22	.824	CES-D × BAI	**−0.19**	0.09	−2.08	**.043**
Peak cortisol (intercept)	**0.73**	0.07	11.04	<**.001**	*Peak cortisol (intercept)*	**0.55**	0.04	14.27	<**.001**
MDD	−0.18	0.09	−1.97	.055	CES-D	−0.01	0.05	−0.29	.772
GAD	−0.06	0.11	−0.52	.609	BAI	**0.12**	0.06	2.13	**.039**
MDD-GAD	−0.10	0.09	−1.08	.285	CES-D x BAI	**−0.14**	0.04	−3.79	**.001**
Afternoon decline (linear)	**−0.05**	0.01	−6.50	<**.001**	*Afternoon decline (linear)*	**−0.03**	0.00	−7.29	<**.001**
MDD	0.02	0.01	1.49	.143	CES-D	**0.01**	0.00	2.08	**.043**
GAD	0.00	0.01	0.20	.843	BAI	−0.01	0.01	−1.91	.063
MDD-GAD	0.01	0.01	0.94	.351	CES-D × BAI	**0.01**	0.00	3.02	**.005**

Note. Abbreviations: BAI=Beck Anxiety Inventory; CAR=cortisol awakening response; CES-D=Center for Epidemiological Studies-Depression; GAD=Generalized Anxiety Disorder alone; MDD=Major Depressive Disorder alone; MDD-GAD=co-occurring MDD-GAD; *SE*=standard error. Bold font denotes statistically significant coefficient (<.05) and associated *p*-value.

[a]Level 2 model; control group is reference group.

[b]Level 2 model; dimensional predictors are standardized.