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Diagnostic and symptom-based predictors of emotional processing in generalized anxiety disorder and major depressive disorder: An event-related potential study

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Abstract

The delineation of specific versus overlapping mechanisms in GAD and MDD could shed light on the integrity of these diagnostic categories. For example, negative emotion generation is one mechanism that may be especially relevant to both disorders. Emotional processing abnormalities were examined among 97 outpatients with generalized anxiety disorder (GAD) or major depressive disorder (MDD) and 25 healthy adults, using the late positive potential (LPP), an event-related potential that is larger for emotional versus neutral stimuli. GAD and MDD were also assessed dimensionally across all participants. Both MDD diagnosis and dimensional depression scores were associated with reduced LPP. When controlling for MDD diagnosis/dimension, both the diagnosis and dimension of GAD were associated with *increased* LPP. Both MDD and GAD dimensions, but not diagnoses, were associated with increased RT to targets that followed emotional pictures. Therefore, MDD and GAD have distinguishable and opposing features evident in neural measures of emotion processing.

Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are two of the most highly comorbid psychiatric disorders. Indeed, more than half of those with GAD have a lifetime diagnosis of MDD (Brown, Campbell, Lehman, Grisham, & Mancill, 2001), and vice-versa (Fava et al., 2000). While high rates of comorbidity might be due in part to shared symptomatology, GAD and MDD also overlap in terms of genetic vulnerability (Kendler, Neale, Kessler, Heath, & Eaves, 1992; Roy, Neale, Pedersen, Mathe, & Kendler, 1995) and response to pharmacological treatment (Gorman, 2002; Rivas-Vazquez, 2001). Because of these and other similarities between GAD and MDD (e.g., common childhood risk; Moffitt

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et al., 2007), there have been calls to reconceptualize GAD and MDD as two manifestations of a single, underlying syndrome, rather than as distinct, categorical disorders (Watson, 2005). Yet despite phenotypic and genotypic similarity, there is also evidence to suggest that GAD and MDD should be considered separate disorders (Mennin, Heimberg, Fresco, & Ritter, 2008), including indications of unique neurochemical (Lydiard & Monnier, 2004) and psychological (e.g., Chelminski & Zimmerman, 2003; Dugas, Buhr, & Ladouceur, 2004) attributes.

Evidence for shared versus unique mechanisms in GAD and MDD could shed light on the similarity or distinctiveness of these diagnostic categories. For instance, negative emotion generation is one mechanism that may be especially relevant to both disorders. Clinical observation and subjective report indicate that both GAD and MDD are characterized by high levels of experienced negative emotion (e.g., Brown, Chorpita, & Barlow, 1998; Clark & Watson, 1991). Furthermore, theories suggest that both anxiety and depression may be characterized by excessive attention to negative information, which may play a role in the development and maintenance of GAD and MDD - e.g., by biasing individuals to overestimate the extent of danger in the environment (Beck, 1976; Bower, 1981; Williams, Watts, MacLeod, & Mathews, 1988).

In the laboratory, behavioral tasks can be used to infer whether GAD and MDD are characterized by excessive attention toward unpleasant stimuli. Some of these tasks rely on the notion that if threatening stimuli capture attention preferentially, then people should locate these stimuli faster. By comparing trials on which rapid attention toward unpleasant stimuli should facilitate as opposed to worsen performance, researchers can estimate the extent to which participants attend preferentially to unpleasant stimuli. Data on the dot-probe task, in which target stimuli appear in place of unpleasant or neutral pictures, suggest that GAD is associated with an attentional bias toward unpleasant stimuli, even when stimuli are presented for as briefly as 14 ms (Mogg, Bradley, & Williams, 1995). Although only a few studies have examined GAD in particular, the broader literature on anxiety suggests that it is characterized by an early and automatic bias toward unpleasant information (Mathews & MacLeod, 2005; Teachman, Joormann, Steinman, & Gotlib, 2012).

In comparison to GAD, there has been relatively inconsistent evidence for increased attention toward unpleasant stimuli in MDD using attentional bias tasks. For instance, using *rapidly* presented unpleasant stimuli, a number of studies have failed to observe increased attention toward unpleasant stimuli in depression (B. P. Bradley, Mogg, & Lee, 1997; Mogg et al., 1995). On the other hand, however, Mathews and colleagues (Mathews, Ridgeway, & Williamson, 1996) found evidence for biased processing of social threat words among depressed individuals when stimuli were presented for longer durations. Therefore, prior work using the dot-probe task suggests that increased attention toward unpleasant stimuli in MDD may be evident primarily at later, more elaborative processing stages (Mathews & MacLeod, 2005; Teachman et al., 2012). In addition, an attentional bias toward unpleasant information in depression may be observed more commonly for idiographic and/or loss-related stimuli as compared to threatening stimuli (e.g., Mathews et al., 1996). Finally, evidence also suggests that comorbid MDD may abolish evidence of an attentional bias toward unpleasant stimuli normally observed in GAD. For instance, Mogg and colleagues

(Mogg et al., 1995) found that an attentional bias toward briefly presented unpleasant stimuli was found only among anxious individuals without comorbid depression (even though both anxiety-relevant and depression-relevant stimuli were used).

Another body of work has examined behavioral *interference* from unpleasant stimuli in GAD and MDD. These tasks rely on the assumption that unpleasant stimuli capture attention preferentially and therefore detract from and slow the processing of task-relevant information. For instance, a number of studies have found evidence of behavioral interference on tasks with unpleasant distracters in both GAD (MacNamara & Hajcak, 2010; Rinck, Becker, Kellermann, & Roth, 2003) and MDD (Wang et al., 2008). Using the emotional Stroop, in which the emotional nature of words is irrelevant to the task, Mogg and colleagues found that individuals with GAD had slower reaction times (RTs) for unpleasant words (Mogg, Bradley, Williams, & Mathews, 1993). This effect was not evident among participants with comorbid depression (B. P. Bradley, Mogg, Millar, & White, 1995), again raising the question as to how comorbid depression affects the processing of unpleasant stimuli in GAD.

Excessive attention toward unpleasant stimuli in GAD and MDD may contribute to heightened affective reactivity in these disorders (Mathews & MacLeod, 2005). Indeed, several studies suggest that GAD (Hilbert, Lueken, & Beesdo-Baum, 2014; Mennin, McLaughlin, & Flanagan, 2009) and MDD (Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2012) are characterized by increased reactivity to unpleasant stimuli. However, the Emotional Context Insensitivity (ECI) theory of depression suggests that MDD might be characterized by *reduced*, rather than heightened, reactivity to unpleasant stimuli. The ECI theory of depression takes an evolutionary view of depression as a defensive motivational state (Nesse, 2000) that arises during times of chronic adversity, and might function to conserve valuable energy resources by promoting disengagement from the environment. According to the ECI view, MDD should be characterized by *attenuated* reactivity to both pleasant and unpleasant stimuli (Rottenberg, Gross, & Gotlib, 2005).

Substantial evidence supports the ECI model of depression (e.g., for a review, see Bylsma, Morris, & Rottenberg, 2007). For instance, individuals with MDD report less subjectively experienced affect when viewing sad or amusing film clips (Rottenberg et al., 2005; Rottenberg, Kasch, Gross, & Gotlib, 2002). MDD has also been associated with reduced emotional modulation of the startle reflex (Dichter & Tomarken, 2008; Dichter, Tomarken, Shelton, & Sutton, 2004; Taylor-Clift, Morris, Rottenberg, & Kovacs, 2011) and with decreased electromyographic facial responding when viewing emotional pictures as compared to healthy adults (HAs; Wexler, Levenson, Warrenburg, & Price, 1994) and patients with other disorders (Gehricke & Shapiro, 2000). Of the studies described above, only two ensured that depressed participants were free from comorbid GAD (Gehricke & Shapiro, 2000; Wexler et al., 1994). Further, only one of the studies described above (Taylor-Clift et al., 2011) examined how comorbid depression modifies affective responding in GAD and other anxiety disorders. In their study, Taylor-Clift and colleagues (2011) found that emotional modulation of the startle reflex was preserved in individuals with anxiety who were free from depression, but was blunted among those with *both* anxiety and depression,

suggesting that the pattern of emotion processing in comorbid anxiety-depression may most closely resemble that observed in depression (i.e., context-insensitivity).

Neurobiological measures may be particularly useful in identifying common and distinct mechanisms within and across disorders (Cuthbert, 2014; Morris & Cuthbert, 2012). For instance, event-related potentials (ERPs) can be used to provide a highly sensitive measure of the processing of emotional stimuli. The late positive potential (LPP) is a positive-going, central-parietal ERP that begins by 300 ms following stimulus onset and is larger for more arousing stimuli – e.g., both pleasant and unpleasant compared to neutral pictures and words (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Dillon, Cooper, Grent-‘t-Jong, Woldoff, & LaBar, 2006; Foti, Hajcak, & Dien, 2009; Schupp et al., 2000). Functionally, the LPP is believed to reflect increased and elaborated attention to stimuli that have been deemed motivationally salient (M. M. Bradley, 2009). In addition to tracking categorical differences in picture emotionality, the LPP is also sensitive to more fine-grained differences in the motivational salience of stimuli. For instance, the LPP is larger to food pictures in participants deprived of food (Stockburger, Schmäzle, Fleisch, Bublatzky, & Schupp, 2009) and to personally salient stimuli such as photographs of one's own relatives or loved ones (Grasso & Simons, 2011; Vico, Guerra, Robles, Vila, & Anllo-Vento, 2010). Therefore, the LPP appears to be modulated by individual differences in the perceived salience of stimuli, which may make it an ideal measure for assessing attention to unpleasant stimulus content in anxiety and depression.

Extant research suggests that GAD may be associated with increased attention toward unpleasant stimuli as assessed using the LPP. For example, MacNamara and Hajcak (2010) had participants with “pure” GAD (i.e., free from comorbid MDD) and a group of HAs perform a task in which the emotional nature of pictures was irrelevant to the primary task. Participants' task was to indicate whether pairs of unpleasant or neutral pictures were the same or different, while ignoring unpleasant or neutral pictures presented in another area of the screen. Participants were only asked to respond to the identity of pictures presented in attended locations, not to the affective nature of these images. Despite the task-irrelevant emotional nature of pictures, individuals with GAD showed greater modulation of the LPP by unpleasant picture content presented in attended locations, compared to the HA group (also see MacNamara & Proudfit, 2014).

Work utilizing the LPP has tended to support the ECI view of depression (for a review, see Proudfit, Bress, Foti, Kujawa, & Klein, 2015). For instance, Foti and colleagues (2010) found that individuals with “pure” MDD (i.e., free from comorbid GAD) showed reduced LPPs to threatening (i.e., angry and fearful) faces compared to HAs. Similar results were observed by Kayser and colleagues (Kayser, Bruder, Tenke, Stewart, & Quitkin, 2000), who, in a study focused on disgust-processing, found that individuals with MDD and/or dysthymia (comorbid diagnoses not reported) showed reduced LPPs to pictures of dermatological disease. There is also evidence to suggest that blunted LPPs might serve as a biomarker of risk for depression in individuals who have not yet developed symptoms: children without depression, whose mothers have a history of depression have been found to exhibit reduced LPPs to emotional faces, when compared to children who are also

depression-free and without maternal history of depression (Kujawa, Hajcak, Torpey, Kim, & Klein, 2012; see also Nelson, Perlman, Hajcak, Klein, & Kotov, 2015).

Together, the work described above raises the possibility that GAD and MDD might be distinguished by opposing affective processes – GAD with larger LPPs and MDD with smaller LPPs. Moreover, these opposing processes could be obscured by high levels of comorbidity frequently observed between these disorders. That is, increased response to unpleasant stimuli in GAD could be concealed by comorbid depression (B. P. Bradley et al., 1995), and vice-versa. However, few studies have examined the processing of unpleasant stimuli simultaneously in individuals diagnosed with GAD or MDD, as well as those with comorbid GAD and MDD (but see Taylor-Clift et al., 2011).

Over the past two decades, interest has grown in the development of dimensional models of psychopathology, which might help explain negative emotion aberrations that are not well accounted for using the current categorical diagnostic system (Clark & Watson, 1991; Krueger & Markon, 2006; Watson, 2009). However, these models have, for the most part, been based on diagnostic and questionnaire data, and have rarely considered neurobiological measures, which are emphasized in the National Institute of Mental Health's Research Domain Criteria initiative (e.g., Morris & Cuthbert, 2012). For instance, few studies have assessed the neurobiology of unpleasant stimulus processing in relation to continuous measures of GAD and MDD symptomatology known to cut across diagnostic boundaries.

In the current study, we assessed the processing of unpleasant and neutral stimuli using neural (LPP) and behavioral (reaction time, RT) measures in a sample of individuals with pure GAD, pure MDD, both GAD and MDD, or no psychiatric diagnosis. Because transdiagnostic dimensions might relate more directly to underlying emotional brain circuits (Cuthbert, 2014; Vaidyanathan, Patrick, & Cuthbert, 2009), we also measured symptoms of GAD and MDD in a continuous fashion across the entire sample. Participants performed a variant of a target categorization task used previously in our lab (Kappenman, MacNamara, & Proudfit, 2014), in which pairs of unpleasant or neutral task-irrelevant pictures were followed by the presentation of a target (i.e., a circle or a square), which appeared in place of one of the previously presented pictures. We expected to observe robust modulation of the LPP by picture type (i.e., unpleasant > neutral), as well as slower RTs for targets presented on unpleasant compared to neutral trials (Kappenman, MacNamara, et al., 2014). We also expected that GAD (diagnosis and dimension) would be associated with increased LPPs to unpleasant versus neutral pictures (MacNamara & Hajcak, 2010; MacNamara & Proudfit, 2014), whereas MDD (diagnosis and dimension) would be associated with reduced LPPs to unpleasant versus neutral pictures (Foti et al., 2010; Kayser et al., 2000; Kujawa et al., 2012). Based on our prior work, we did not expect to observe any group differences in RT (MacNamara & Hajcak, 2010).

Method

Participants

Participants were drawn from an initial sample of 344 individuals 18 years of age or older, who took part in the Reclassification of Mood and Anxiety Psychopathology (ReMAP)

project. ReMAP recruited patients from outpatient psychology and psychiatry clinics, and psychologically healthy adults (HAs) from medical clinics (all clinics were located in Suffolk County, NY). Patients were eligible for the study if they were seeking treatment for a psychiatric problem. HAs were eligible for the study if they were receiving outpatient medical treatment for a chronic physical condition (e.g., diabetes, heart disease) and were free from lifetime Axis I psychopathology (with the exception of specific phobias, which were allowed); therefore, like the patients, HAs suffered from impairment in some aspect of their life, but were free from psychiatric diagnoses. Adequate English language comprehension was required of all participants.

The current analyses are focused on data from all ReMAP patients who met the following inclusion and exclusion criteria ($n = 97$). Patients were required to meet criteria for Generalized Anxiety Disorder (GAD) or Major Depressive Disorder (MDD). Diagnoses were made according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 2007), which assesses for the presence of GAD in the past six months and MDD in the past month. Comorbidities were permitted, with the exception of a lifetime diagnosis of bipolar disorder or active psychosis; psychiatric medications were allowed. Diagnostic assessments were made by five Master's level clinicians who were trained using SCID-I videos, and who received supervision and feedback from one of the senior authors (RK). Using 21 interviews from these clinicians, kappa coefficients for each of GAD and MDD diagnoses were 1.00. For diagnostic comparison and to ensure a broad range of symptom severity, we also included all HAs who participated in ReMAP and completed the target categorization task ($n = 25$).

These inclusion and exclusion criteria yielded an initial sample of $N = 122$ participants (97 patients; 25 HAs). Of these, 8 participants (6 patients; 2 HAs) were excluded from ERP and RT analyses because they performed worse than chance on the target identification task (i.e., $< 50\%$ accuracy), or behavioral data were unavailable due to technical difficulties. An additional 3 participants (all patients) were excluded because of poor quality EEG recordings that would have required rejection of more than 50% of trials. This left a total of $n = 111$ participants for all analyses, whose demographic characteristics are presented in Table 1. Of these, 23 participants had neither GAD nor MDD (HAs), 22 had a diagnosis of GAD but not MDD, 36 had a diagnosis of MDD but not GAD and 30 had a diagnosis of both GAD and MDD. Because of controversy over the DSM-IV (APA, 2000) hierarchical rule, in which GAD is not diagnosed if it occurs exclusively within the course of a mood disorder (e.g., Andrews et al., 2010; Lawrence, Liverant, Rosellini, & Brown, 2009; Zimmerman & Chelminski, 2003), we also performed alternative analyses in which diagnosis of GAD was made while ignoring this criterion. Informed consent was obtained from all participants. Study procedures were approved by the Stony Brook University Institutional Review Board.

Materials

The stimuli were 40 neutral and 40 unpleasant IAPS images¹. Neutral images included pictures of buildings, household objects and people with neutral facial expressions.

Unpleasant images included pictures of animals attacking the viewer, assault and abduction scenes and mutilated bodies.

The Interview for Mood and Anxiety Symptoms (IMAS; Kotov, Perlman, Gámez, & Watson, 2015) is a structured interview measure of DSM-IV anxiety and mood disorder symptoms in the past month. There are no skip-outs in the IMAS; all questions are asked of each participant, and symptom coverage in the IMAS is more comprehensive than in the SCID. Items are scored on a 3-point scale (0 = absent; 1 = subthreshold; 2 = above threshold) and then summed to create composite indices. There are 10 primary scales, corresponding to each anxiety disorder, overall depression syndrome (including symptoms of MDD and dysthymia), mania, and irritability, with each scale showing clear convergent and discriminant validity (Kotov et al., 2015; Watson et al., 2012; Watson, Clark, Chmielewski, & Kotov, 2013). We used the IMAS Generalized Anxiety and IMAS Depression scales in order to assess GAD- and MDD-related symptomatology continuously across the whole sample. Ratings required depression symptoms to be present for “at least several days” in the past month; generalized anxiety symptoms had to be present for “more than half the month.” The IMAS was administered by lay interviewers, each of whom completed a 20-hr training program and was certified based on observation of interviews and reliability of ratings. The training included modules on establishing rapport, distinguishing between clinically significant and normative responses, probing techniques, and the specific content of the IMAS. Internal consistency reliability of these scales was excellent ($\alpha = .95$ for IMAS Depression and $.89$ for IMAS Generalized Anxiety); interrater reliability was also high (intraclass correlation $.96$ to $.98$; Ruggero et al., 2014).

Task

Participants performed a target classification task. An example trial sequence is presented in Figure 1. Stimuli were presented on a black background using an LCD monitor viewed at a distance of approximately 60 cm. On each trial, a pair of identical unpleasant or neutral IAPS images (each subtending approximately 6×8 degrees of visual angle) was presented in color for 250 ms, arranged vertically (i.e., one image above and one below the center of the screen). Following the offset of the images, a white fixation cross was presented centrally for 50 ms; next, a target composed of a white circle or a square (approximately $.75 \times .75$ degrees of visual angle) was presented for 50 ms, centered in the location of one of the previously presented images. Participants made a key press using the index or middle finger of the right hand to indicate whether the target item was a circle or a square; the mapping of targets and response buttons was counterbalanced across participants. Participants were given a window of up to 1,200 ms from the offset of the target to respond; the response window ended when a response was made. Immediately following the response, a jittered intertrial interval of 1,000-1,500 ms occurred, in which a white fixation cross was presented in the center of the screen. Participants were told that the images were irrelevant to the task

¹IAPS pictures were: unpleasant - 1050, 1120, 1275, 1300, 1302, 1930, 1932, 2120, 2811, 2810, 3030, 3051, 3060, 3100, 3102, 3120, 3140, 3160, 3170, 3225, 3400, 3550, 6190, 6200, 6250, 6260, 6313, 6315, 6350, 6370, 6510, 6540, 6560, 6570, 9040, 9253, 9301, 9320, 9405, 9594 and neutral - 1450, 1670, 2102, 2190, 2191, 2200, 2214, 2305, 2357, 2383, 2397, 2512, 2745, 5530, 5534, 6150, 7000, 7002, 7004, 7009, 7030, 7034, 7037, 7040, 7054, 7057, 7080, 7130, 7140, 7175, 7491, 7493, 7500, 7546, 7547, 7550, 7560, 7595, 7620, 7920.

but that they should keep their eyes onscreen at all times; they were instructed to respond as quickly and accurately as possible to the targets.

Participants completed 80 trials. Unpleasant and neutral trial types were randomly intermixed: there were 40 trials on which two identical neutral images were presented and 40 trials on which two identical unpleasant images were presented. Target type (i.e., a circle or a square) was fully counterbalanced for each trial type, and targets were presented an equal number of times above and below fixation. Images were not repeated. A short, self-paced break was provided halfway through the experiment.

Electroencephalographic recording

Continuous EEG was recorded using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). Thirty-four electrode sites (standard 32 channel setup, as well as FCz and Iz) were used, based on the 10/20 system; in addition, electrodes were placed on the left and right mastoids. The electrooculogram (EOG) generated from eyeblinks and eye movements was recorded from four facial electrodes - vertical eye movements and blinks were measured with two electrodes, placed approximately 1 cm above and below the right eye; horizontal eye movements were measured using two electrodes, placed approximately 1 cm beyond the outer edge of each eye. The EEG signal was pre-amplified at the electrode to improve the signal-to-noise ratio. The EEG and EOG were low-pass filtered using a fifth order sinc filter with a half-power cutoff at 204.8 Hz and then digitized at 1024 Hz with 24 bits of resolution. The voltage from each active electrode was referenced online, with respect to a common mode sense (CMS) active electrode producing a monopolar (i.e., non-differential) channel.

Data reduction and analysis

Analyses were performed using Brain Vision Analyzer software (Brain Products, Gilching, Germany). Data were re-referenced offline, to the average of the two mastoids, and band-pass filtered from 0.1 to 30 Hz. Following the segmentation of data (see below), eye blink and ocular corrections were made according to the method developed by Miller, Gratton and Yee (1988). Artifact analysis was used to identify a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100 ms intervals. Trials were also inspected visually for any remaining artifacts, and data from individual channels containing artifacts were rejected on a trial-by-trial basis. The percentage of trials with artifacts on channels included in the LPP pooling (described below) did not differ by condition [$t(110) = .77, p = .44$; unpleasant trials, $M = 1.08\%$, $SD = 2.75\%$; neutral trials, $M = .90\%$, $SD = 2.48\%$].

To construct ERPs, the EEG was segmented for each trial beginning 200 ms prior to picture onset and continuing for 1,200 ms (i.e., until 1,000 ms after picture onset). Baseline correction for each trial used the 200 ms prior to picture onset. The LPP was scored by averaging amplitudes at pooling, CP1, CP2, Cz and Pz from 400-1,000 ms after picture onset, in line with prior work (e.g., MacNamara & Hajcak, 2009).

RT was the time it took participants to respond following target onset. Both RT and LPP measures were analyzed on correct trials only. Because we wanted to examine the degree to

which GAD and MDD were associated with differential responding to unpleasant versus neutral pictures, we calculated residual scores reflecting this difference (separately for RT and LPP) for each participant. We chose to use residual scores instead of difference scores (i.e., unpleasant minus neutral) because residual scores are more effective at isolating variance unique to a particular condition. Whereas difference scores remain correlated with initial values (i.e., average responses to each of the unpleasant and neutral pictures; Cronbach & Furby, 1970; Dubois, 1957), residual scores do not; moreover, residuals may be a more reliable means of measuring the extent to which individuals differentiate unpleasant from neutral pictures (Weinberg, Venables, Proudfit, & Patrick, 2014). To create residual scores, two regressions were performed, predicting RT to unpleasant pictures from RT to neutral pictures and predicting the LPP to unpleasant pictures from the LPP to neutral pictures. Unstandardized residuals representing variance unique to unpleasant pictures after controlling for the response to neutral pictures were saved for each participant and from each regression. These residual scores were used in subsequent analyses, and are referred to from here on as RT and LPP.

We used linear regression to examine associations of RT and LPP with MDD and GAD diagnoses, as well as associations between each of RT and LPP and IMAS Depression, IMAS Generalized Anxiety². Next, both diagnoses and symptoms were entered as predictors in the same regression, to determine whether variance in RT and LPP was better accounted for by diagnosis, symptomatology, or both. Statistical analyses were performed using SPSS (Version 20.0) General Linear Model software.

Results

IMAS Depression scores were strongly associated with a diagnosis of MDD (as assessed using the SCID; $d = 2.95$), and moderately to strongly associated with a diagnosis of GAD ($d = .57$ when assessed using the DSM-IV hierarchical criterion; $d = .80$ without the hierarchical criterion). IMAS Generalized Anxiety, however, was strongly associated with a diagnosis of MDD ($d = 2.40$) and moderately to strongly associated with a diagnosis of GAD ($d = .67$ when using the DSM-IV hierarchical criterion; $d = .90$ without the hierarchical criterion). IMAS Generalized Anxiety and IMAS Depression were strongly correlated [$r(109) = .88, p < .001$].

Participants performed well on the task ($M = 88.42\%$ correct, $SD = 10.30$; range = 55%-100% correct). Across participants, there was no difference between accuracy on trials with unpleasant compared to neutral pictures [$t(110) = .76, p = .45$; neutral pictures, $M = 88.69\%$, $SD = 10.46$; unpleasant pictures, $M = 88.15\%$, $SD = 11.43$]. Participants were slower to respond on trials with unpleasant compared to neutral pictures [$t(110) = 1.96, p = .05$; neutral pictures, $M = 615.27$ ms, $SD = 10.14$; unpleasant pictures, $M = 622.20$ ms, $SD = 10.09$], and unpleasant compared to neutral pictures elicited larger LPPs [$t(110) = 3.97, p < .001$; neutral pictures, $M = 2.21$ μ v, $SD = 2.87$; unpleasant pictures, $M = 3.04$ μ v, $SD = 2.85$]. All subsequent analyses were performed using RT and LPP.

²Addition of the following variables did not substantially alter results: a) interaction terms for GAD $\times$ MDD diagnoses and IMAS Generalized Anxiety $\times$ IMAS Depression; b) medication class and c) other anxiety and depressive diagnostic comorbidities.

GAD and MDD Diagnoses

To examine relationships between GAD, MDD, RT and LPP, we coded the presence or absence of GAD (0=no, 1=yes) and MDD (0=no, 1=yes) for each participant. Next, we entered these dichotomous variables, in turn, into a stepwise linear regression predicting

RT. Results showed that GAD alone was not associated with RT [$R^2 = .00$, $F(1, 109) = .23$, $p = .64$; $\beta = .04$]; neither was MDD [$R^2 = .03$, $F(1, 109) = 3.26$, $p = .07$; $\beta = .17$]. Next, we entered both GAD and MDD into the model simultaneously [$R^2 = .03$, $F(2, 108) = 1.77$, $p = .18$]. Results showed that when controlling for the relationship between MDD diagnosis and RT, the association with GAD was still non-significant ($\beta = .05$, $p = .59$). When controlling for the relationship between GAD diagnosis and RT, the effect of MDD also remained nonsignificant ($\beta = .17$, $p = .07$). When ignoring the DSM-IV hierarchical criterion for GAD (APA, 2000), 10 participants who previously only met criteria for MDD were given a diagnosis of GAD. Using this diagnosis, as in the initial analysis, GAD was not associated with RT [$R^2 = .00$, $F(1, 109) = .58$, $p = .45$; $\beta = .07$]. When both GAD and MDD were entered into the model [$R^2 = .03$, $F(2, 108) = 1.80$, $p = .17$], neither predictor reached significance (GAD: $\beta = .06$, $p = .56$; MDD: $\beta = .16$, $p = .09$), as in the initial analyses.

Parallel analyses for LPP showed that separately, GAD diagnosis was not associated with LPP [$R^2 = .01$, $F(1, 109) = .61$, $p = .44$; $\beta = .08$]; MDD, on the other hand, was associated with attenuated LPP [$R^2 = .05$, $F(1, 109) = 5.49$, $p = .02$; $\beta = -.22$; Figure 2]. In a subsequent step, we entered both GAD and MDD in the model simultaneously [$R^2 = .05$, $F(2, 108) = 3.00$, $p = .05$]. When controlling for MDD, the association between GAD and the LPP was still non-significant ($\beta = .07$, $p = .47$). When controlling for the relationship between GAD diagnosis and the LPP, MDD was still associated with reduced LPP ($\beta = -.22$, $p = .02$). When ignoring the DSM-IV hierarchical criterion (APA, 2000), GAD was still not associated with LPP [$R^2 = .03$, $F(1, 109) = 2.98$, $p = .09$; $\beta = .16$]. However, when both GAD and MDD were entered into the model simultaneously [$R^2 = .08$, $F(2, 108) = 4.86$, $p = .01$], GAD was associated with increased LPP ($\beta = .19$, $p = .046$) and MDD was still associated with reduced LPP ($\beta = -.24$, $p = .01$).

GAD and MDD Symptomatology

To examine relationships between continuous measures of GAD and MDD symptomatology and each of RT and LPP, we performed a series of linear regressions. First, we entered IMAS Generalized Anxiety and IMAS Depression into separate linear regressions predicting

RT. Results showed that higher IMAS Generalized Anxiety scores were associated with greater RT – i.e., increased slowing to unpleasant pictures [$R^2 = .05$, $F(1, 109) = 5.58$, $p = .02$; $\beta = .22$]; higher IMAS Depression scores were also associated with greater RT [$R^2 = .04$, $F(1, 109) = 4.05$, $p = .05$; $\beta = .19$]. Next, we entered both IMAS Generalized Anxiety and IMAS Depression into the model simultaneously. Results did not reach significance [$R^2 = .05$, $F(2, 108) = 2.77$, $p = .07$; IMAS Generalized Anxiety with $\beta = .24$, $p = .23$; IMAS Depression with $\beta = -.03$, $p = .89$].

When IMAS Generalized Anxiety and IMAS Depression were entered into separate linear regressions predicting LPP, results showed that IMAS Generalized Anxiety was not associated with LPP [$R^2 = .01$, $F(1, 109) = .86$, $p = .36$; $\beta = -.09$]; however, higher IMAS-

Depression scores were associated with reduced LPP [$R^2 = .04$, $F(1, 109) = 5.01$, $p = .03$; $\beta = -.21$]. When IMAS Generalized Anxiety and IMAS Depression were entered into the model simultaneously, both IMAS scales were associated with LPP [$R^2 = .09$, $F(2, 108) = 5.17$, $p = .007$]. ERP waveforms and topographic maps depicting these effects are presented in Figure 3. When controlling for the association of depressive symptoms with the LPP, GAD symptoms were associated with increased LPP ($\beta = .45$, $p = .02$). When controlling for the association between GAD symptoms and the LPP, depressive symptoms continued to be associated with reduced LPP ($\beta = -.61$, $p = .003$).

Finally, we simultaneously entered the continuous symptom measures (i.e., IMAS Generalized Anxiety and IMAS Depression scores) and diagnostic ratings (presence/absence of GAD and MDD) into a) a linear regression predicting RT and b) a linear regression predicting LPP. These analyses allowed us to determine whether a dimensional or categorical approach to description of these conditions was better at accounting for variance in RT and LPP. For RT, we found that the overall model did not reach significance [$R^2 = .05$, $F(4, 106) = 1.38$, $p = .24$] and neither did any of the predictors, diagnostic or symptom-based (Current GAD with $\beta = -.03$, $p = .79$; Current MDD with $\beta = -.01$, $p = .96$; IMAS Generalized Anxiety with $\beta = .26$, $p = .23$; IMAS Depression with $\beta = -.03$, $p = .79$). For LPP, the overall model was significant [$R^2 = .10$, $F(4, 106) = 3.03$, $p = .02$]. Furthermore, IMAS Generalized Anxiety was associated with increased LPP ($\beta = .45$, $p = .03$) and IMAS Depression was associated with reduced LPP ($\beta = -.51$, $p = .03$). Diagnostic predictors were not significant (Current GAD with $\beta = .07$, $p = .55$; Current MDD with $\beta = -.14$, $p = .47$).

Next, we entered the continuous symptom measures and diagnoses - made without using the hierarchical rule-out for GAD - into linear regressions predicting a) RT and b) LPP. For RT, we found that the overall model still did not reach significance [$R^2 = .05$, $F(4, 106) = 1.37$, $p = .25$] and neither did any of the predictors, diagnostic or symptom-based (Current GAD with $\beta = -.15$, $p = .89$; Current MDD with $\beta = .01$, $p = .97$; IMAS Generalized Anxiety with $\beta = .25$, $p = .24$; IMAS Depression with $\beta = -.03$, $p = .90$). For LPP, the overall model was significant [$R^2 = .14$, $F(4, 106) = 4.32$, $p = .003$]. IMAS Generalized Anxiety was no longer associated with increased LPP ($\beta = .38$, $p = .06$), however IMAS Depression was still associated with reduced LPP ($\beta = -.61$, $p = .01$). A diagnosis of GAD was associated with increased LPP ($\beta = .24$, $p = .03$); the association with MDD was still non-significant ($\beta = -.03$, $p = .87$)².

Discussion

We investigated behavioral and ERP measures of unpleasant picture processing in relation to diagnostic and continuous symptom measures of GAD and MDD. Behaviorally, both GAD and MDD were associated with increased slowing in response to unpleasant compared to neutral pictures. Using the LPP, results supported the ECI view of depression and the negative potentiation view of GAD. That is, a diagnosis of MDD was associated with less emotional modulation of the LPP, and - when controlling for the influence of MDD and ignoring the DSM-IV hierarchical rule (APA, 2000) - GAD was associated with increased emotional modulation of the LPP. Likewise, greater symptoms of MDD were associated

with less emotional modulation of the LPP, whereas greater GAD symptomatology was associated with greater negative potentiation of the LPP – when controlling for the influence of MDD symptomatology. The results suggest that the LPP may yield neural signatures of distinct and opposing patterns of emotion-processing in relation to GAD and MDD. If MDD affects associations between GAD and the LPP, this suggests that GAD and MDD should not be considered redundant concepts (Weinberg, Klein, & Hajcak, 2012). Moreover, MDD comorbidity may obscure understanding of affective mechanisms associated with these disorders.

The current study adds to the literature linking a reduced LPP to MDD (Foti et al., 2010; Kayser et al., 2000; Kujawa et al., 2012). Moreover, the data also suggest that depression-related affective blunting is not affected by, and persists even when controlling for, the presence of GAD (at both diagnostic and symptom levels). Of note, however, our results are seemingly in contrast to a number of fMRI studies which have found evidence of increased amygdala reactivity to negative stimuli in MDD (Groenewold et al., 2012; Hamilton et al., 2012; but see Diener et al., 2012). Differences in results may be explained in part by differences between the amygdala, which responds and habituates rapidly to salient stimuli (Cheng, Richards, & Helmstetter, 2007; Wright et al., 2001), and the LPP, which measures elaborated stimulus processing and is relatively insensitive to the effects of habituation (Codispoti, Ferrari, & Bradley, 2007; Hajcak, MacNamara, & Olvet, 2010). More work is needed to reconcile differences observed across these and other measures of affective stimulus processing in MDD (e.g., Bylsma et al., 2007).

Negative emotion potentiation of the LPP in GAD has been observed in prior work that used a relatively “clean” sample (i.e., no comorbid depression; MacNamara & Hajcak, 2010); the current study further suggests that GAD-related increases in the LPP may be obscured if comorbid depression is not accounted for. However, the present results contradict a prior study from our lab (Weinberg & Hajcak, 2011), which found evidence of *reduced* LPPs to unpleasant compared to neutral stimuli in GAD. Importantly, the speeded response task used here was more similar to work that *has* found evidence of negative emotion potentiation in GAD (i.e., MacNamara & Hajcak, 2010). In the paradigm used by Weinberg and Hajcak (2011), pictures were passively viewed, task-relevant, blocked by valence, and presented for a longer presentation duration (i.e., 1.5 seconds). When pictures are presented for longer durations, as in Weinberg and Hajcak's (2011) study, individuals with GAD may initially engage in increased, early processing of unpleasant stimuli³, after which they may direct their attention away from arousing picture content, for example, by thinking about something else or focusing on less arousing portions of the picture. By contrast, when unpleasant pictures are presented rapidly, without warning, and for only brief durations – as in the present study and in MacNamara and Hajcak (2010) – individuals with GAD may be less able to engage in top-down (i.e., goal-driven) reductions in picture processing, and evidence of negative potentiation may be observed. Additionally, it is possible that rapid tasks in which participants are required to make a behavioral response might increase

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³Indeed, Weinberg and Hajcak (2011) found evidence of an increased early ERP (the P1) to unpleasant stimuli in GAD.

anxiety among participants with GAD, who could be especially concerned about their performance.

Prior failures to observe evidence of negative emotion potentiation in GAD (e.g., Mochcovitch, da Rocha Freire, Garcia, & Nardi, 2014) might also be due, in part, to the presence of high levels of comorbid depression not controlled for in analyses (see also Weinberg et al., 2012). In the present study, IMAS Generalized Anxiety and IMAS Depression scores were strongly and positively correlated with each other and a diagnosis of depression in particular was characterized by high levels of both anxious and depressive symptoms, which may reflect elevated levels of general distress (Clark & Watson, 1991). Yet despite close associations between GAD and MDD, the syndromes showed a clearly distinct pattern of correlations with neural measures, indicating that although these conditions have much in common, each includes unique features that can act in opposite ways (see also Beesdo et al., 2009; Etkin & Schatzberg, 2011; Heller, 1998; Weinberg et al., 2012). In sum, the absence of negative potentiation among individuals who were highly depressed cannot be attributed to low levels of GAD symptomatology. Instead, depressive symptoms seem to exert a unique, suppressive effect on negative emotion processing in relation to GAD symptoms, and this effect was sufficient to obscure evidence of GAD-related increases in the LPP.

According to the DSM-IV (APA, 2000), a diagnosis of GAD cannot be made if an individual meets criteria for GAD only within the context of a mood disorder. This hierarchical criterion is intended to avoid overdiagnosis of GAD, which shares several features with MDD (i.e., 4 of 6 GAD symptoms – sleep difficulty, difficulty concentrating, restlessness and fatigue -are also symptoms of MDD). However, the hierarchical criterion may disguise true rates of GAD-MDD comorbidity, and may lead to the loss of information relevant to the characterization and treatment of patients (Lawrence et al., 2009; Zimmerman & Chelminski, 2003). In the current study, a diagnosis of GAD and symptoms of GAD were found to have similar relationships with the LPP *only* when the hierarchical criterion was ignored. Therefore, when diagnosis of GAD is made without using the hierarchical rule, it seems to function similarly to a dimensional measure of GAD and seems to map better on to underlying neurobiology than diagnoses made using this rule.

Continuous measures of symptomatology were better predictors of behavior than were categorical diagnoses: symptoms of both MDD and GAD were associated with increased behavioral slowing for unpleasant compared to neutral stimuli (whereas no effects were observed for diagnoses, even when ignoring the hierarchical criterion for GAD). GAD- and MDD-related slowing has been observed in prior work, using the visual search or target identification tasks (Rinck et al., 2003; Wang et al., 2008) and the emotional Stroop task (Becker, Rinck, Margraf, & Roth, 2001; Chen et al., 2013; Kerr, Scott, & Phillips, 2005). Here, symptoms of GAD and MDD were behaviorally identical, but showed opposite influences on the LPP. What could be driving this dissimilarity in effects across behavioral and neural measures?

One possibility is that behavioral slowing in GAD and MDD may be unrelated to attentional processes captured by the LPP. For instance, slower responses in both GAD and MDD might

reflect psychomotor slowing and/or a more cautious response strategy resulting from heightened negative affect common to both disorders. In addition, unpleasant stimuli might give rise to unrelated or ruminative thoughts in depression, which could compete for processing resources with task-relevant stimuli (Mogg, Holmes, Garner, & Bradley, 2008), or, depressed participants might have willfully diverted attention away from unpleasant pictures, resulting in smaller LPPs and slower RTs.

In addition, it is important to recognize differences between ERP and behavioral measures. ERPs that are time-locked to picture onset provide a *direct* assessment of neural activity reflecting attention to unpleasant stimuli. Behavioral measures, however, reflect the summation of a number of distinct mental processes that occur between the onset of a stimulus and the execution of a behavioral response. This is especially true for target detection tasks, in which participants do not respond directly to emotional stimuli, but to targets that appear in place of - and several hundred ms after - emotional stimuli. Therefore, because ERPs provide a relatively more direct measure of attention to unpleasant pictures, they may reveal different disorder-related aberrations than are evident when using measures that are taken further “downstream” (e.g., RT). Further, behavioral measures typically have worse psychometric properties than ERPs. For instance, prior work using target detection tasks have found RT to be unreliable (Kappenman, MacNamara, et al., 2014; Schmukle, 2005; Staugaard, 2009; Waechter, Nelson, Wright, Hyatt, & Oakman, 2013); using the same task, however, ERPs are reliable (Kappenman, Farrens, Luck, & Proudfit, 2014; Kappenman, MacNamara, et al., 2014). Any of these explanations, or a combination of factors could explain why we observed different results for the LPP and RT, though these hypotheses await confirmation in future work. Importantly, however, behavioral slowing is typically thought to arise from increased attention towards unpleasant stimuli, yet the current results do not, at face value, support this interpretation for depressed individuals, who showed both smaller LPPs and slower RTs on unpleasant trials.

To make sense of the opposing patterns of neural reactivity observed in relation to GAD (associated with larger LPPs) and MDD (associated with smaller LPPs), a functional perspective might be considered (Mennin et al., 2008). Chronologically, GAD typically occurs before depression, and – more than any other anxiety disorder - a diagnosis of GAD predisposes an individual to acquiring a diagnosis of MDD (Kessler, Walters, & Wittchen, 2004). The ECI view suggests that depression may be a response to chronic adversity that serves to conserve valuable energy resources by promoting disengagement from the environment (Nesse, 2000). Therefore, individuals with GAD might be characterized by hyper-reactivity to negative stimuli early on during the course of the disorder, but might transition over time (i.e., later on during the disorder) to a state of defensive disengagement more characteristic of depression. Future work could test this hypothesis by examining individuals with GAD who have never experienced depression longitudinally, in order to increase understanding of relationships between GAD, reactivity to unpleasant stimuli and depressive symptoms. Future work might also consider including pleasant pictures in order to test the hypothesis that MDD should be associated with reduced reactivity to both positively and negatively valenced emotional stimuli (Rottenberg et al., 2005), and to examine specificity for LPP potentiation to unpleasant pictures in GAD (Sass et al., 2009).

The current study was limited in some respects. First, we used unpleasant pictures that were primarily high-arousing and not idiographic. Future work may wish to determine whether different results are obtained when using disorder-specific pictures (e.g., depictions of threat versus loss) or when idiographic stimuli are selected for each participant. Second, pictures in the current study were presented very rapidly; future work may wish to investigate whether increased processing of unpleasant stimuli in MDD is observed if longer stimulus presentation durations are used (i.e., facilitating elaborative processing). Third, all participants in the current study were treatment-seeking: patients were receiving treatment for psychiatric problems, and HAs were receiving treatment for ongoing medical conditions (e.g., heart disease, diabetes). Therefore, controls and patients were matched on outpatient status, and variability within the control group may have been likely greater than for studies using groups of “super controls” who are not undergoing treatment of any kind. This however, may limit generalizability of the present findings to the general population. Fourth, behavioral findings were not predicted, which limits their interpretability.

Ultimately, emotion dysregulation in GAD and MDD could result from either aberrant emotional reactivity and/or deficient regulatory control (or a combination of the two). While these processes are difficult to separate, the present results suggest that emotion dysregulation in GAD and MDD may originate, at least in part, from abnormal emotion generation. Therefore, assessment procedures that distinguish between emotion generation and emotion regulatory aberrations might be helpful in clarifying the contribution of each of these processes to a patient's overall pattern of emotion dysregulation (Rottenberg & Gross, 2006). In addition, treatment targets will likely differ depending on whether aberrations are observed in one of both of these systems. For instance, evidence of emotional blunting might suggest the need to increase patient emotional engagement and decrease avoidance prior to beginning exposure therapy for anxiety.

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References

- Andrews G, Hobbs MJ, Borkovec TD, Beesdo K, Craske MG, Heimberg RG, Stanley MA. Generalized worry disorder: a review of DSM-IV generalized anxiety disorder and options for DSM-V. *Depression and Anxiety*. 2010; 27(2):134–147. <http://doi.org/10.1002/da.20658>. [PubMed: 20058241]
- APA. *Diagnostic and statistical manual of mental disorders IV-TR*. 4th, text rev. Washington, DC: Amer Psychiatric Pub Inc; 2000.
- Beck, AT. *Cognitive therapy and the emotional disorders*. New York: International Universities Press; 1976.
- Becker ES, Rinck M, Margraf J, Roth WT. The emotional Stroop effect in anxiety disorders: general emotional or disorder specificity? *Journal of Anxiety Disorders*. 2001; 15(3):147–159. [PubMed: 11442135]
- Beesdo K, Lau JYF, Guyer AE, McClure-Tone EB, Monk CS, Nelson EE, et al. Pine DS. Common and Distinct Amygdala-Function Perturbations in Depressed vs Anxious Adolescents. *Archives of General Psychiatry*. 2009; 66(3):275–285. <http://doi.org/10.1001/archgenpsychiatry.2008.545>. [PubMed: 19255377]

- Bower GH. Mood and memory. *American Psychologist*. 1981; 36:129–148. [PubMed: 7224324]
- Bradley BP, Mogg K, Lee SC. Attentional biases for negative information in induced and naturally occurring dysphoria. *Behaviour Research and Therapy*. 1997; 35:911–927. [PubMed: 9401132]
- Bradley BP, Mogg K, Millar N, White J. Selective processing of negative information: Effects of clinical anxiety, concurrent depression, and awareness. *Journal of Abnormal Psychology*. 1995; 104:532–536. [PubMed: 7673577]
- Bradley MM. Natural selective attention: orienting and emotion. *Psychophysiology*. 2009; 46(1):1–11. <http://doi.org/10.1111/j.1469-8986.2008.00702.x>. [PubMed: 18778317]
- Brown TA, Campbell LA, Lehman CL, Grisham JR, Mancill RB. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. *Journal of Abnormal Psychology*. 2001; 110:585–599. [PubMed: 11727948]
- Brown TA, Chorpita BF, Barlow DH. Structural relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. *Journal of Abnormal Psychology*. 1998; 107(2):179–192. [PubMed: 9604548]
- Bylsma LM, Morris BH, Rottenberg J. A meta-analysis of emotional reactivity in major depressive disorder. *Clinical Psychology Review*. 2007; 28:676–691. [PubMed: 18006196]
- Chelminski I, Zimmerman M. Pathological worry in depressed and anxious patients. *Journal of Anxiety Disorders*. 2003; 17:533–546. [PubMed: 12941364]
- Cheng DT, Richards J, Helmstetter FJ. Activity in the human amygdala corresponds to early, rather than late period autonomic responses to a signal for shock. *Learning & Memory*. 2007; 14(7):485–490. <http://doi.org/10.1101/lm.632007>. [PubMed: 17626906]
- Chen J, Wang Z, Wu Y, Cai Y, Shen Y, Wang L, Shi S. Differential attentional bias in generalized anxiety disorder and panic disorder. *Neuropsychiatric Disease and Treatment*. 2013; 9:73–80. <http://doi.org/10.2147/NDT.S36822>. [PubMed: 23326197]
- Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology*. 1991; 100:316–336. [PubMed: 1918611]
- Codispoti M, Ferrari V, Bradley MM. Repetition and event-related potentials: Distinguishing early and late processes in affective picture perception. *Journal of Cognitive Neuroscience*. 2007; 19:577–586. [PubMed: 17381249]
- Cronbach LJ, Furby L. How we should measure “change”: Or should we? *Psychological Bulletin*. 1970; 74(1):68–80. <http://doi.org/10.1037/h0029382>.
- Cuthbert BN. Translating intermediate phenotypes to psychopathology: The NIMH Research Domain Criteria. *Psychophysiology*. 2014; 51(12):1205–1206. <http://doi.org/10.1111/psyp.12342>. [PubMed: 25387702]
- Cuthbert BN, Schupp HT, Bradley MM, Birbaumer N, Lang PJ. Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology*. 2000; 52:95–111. [http://doi.org/doi:10.1016/S0301-0511\(99\)00044-7](http://doi.org/doi:10.1016/S0301-0511(99)00044-7). [PubMed: 10699350]
- Dichter GS, Tomarken AJ. The Chronometry of Affective Startle Modulation in Unipolar Depression. *Journal of Abnormal Psychology*. 2008; 117(1):1–15. <http://doi.org/10.1037/0021-843X.117.1.1>. [PubMed: 18266482]
- Dichter GS, Tomarken AJ, Shelton RC, Sutton SK. Early- and late-onset startle modulation in unipolar depression. *Psychophysiology*. 2004; 41:433–440. [PubMed: 15102129]
- Diener C, Kuehner C, Brusniak W, Ubl B, Wessa M, Flor H. A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *Neuroimage*. 2012; 61:677–685. [PubMed: 22521254]
- Dillon DG, Cooper JJ, Grent-t-Jong T, Woldoff MG, LaBar KS. Dissociation of event-related potentials indexing arousal and semantic cohesion during emotional word encoding. *Brain and Cognition*. 2006; 62:43–57. [PubMed: 16678953]
- Dubois, PH. Multivariate correlational analysis. Vol. xv. Oxford, England: Harper; 1957.
- Dugas, MJ.; Buhr, K.; Ladouceur, R. The role of intolerance of uncertainty in etiology and maintenance. In: Heimberg, RG.; Turk, CL.; Mennin, DS., editors. *Generalized anxiety disorder: advances in research and practice*. New York: Guilford Press; 2004. p. 142–163.

- Etkin A, Schatzberg AF. Common Abnormalities and Disorder-Specific Compensation During Implicit Regulation of Emotional Processing in Generalized Anxiety and Major Depressive Disorders. *American Journal of Psychiatry*. 2011; 168:968–978. [PubMed: 21632648]
- Fava M, Rankin MA, Wright EC, Alpert JE, Nierenberg AA, Pava J, Rosenbaum JF. Anxiety disorders in major depression. *Comprehensive Psychiatry*. 2000; 41:97–102. [PubMed: 10741886]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, J.B.W. Structured Clinical Interview for DSM-IV-TR axis I disorders research version, patient edition with psychotic screen. New York: Biometrics Research, New York State Psychiatric Institute; 2007.
- Foti D, Hajcak G, Dien J. Differentiating neural responses to emotional pictures: Evidence from temporal-spatial PCA. *Psychophysiology*. 2009; 46:521–530. <http://doi.org/doi:10.1111/j.1469-8986.2009.00796.x>. [PubMed: 19496228]
- Foti D, Olvet DM, Klein DN, Hajcak G. Reduced electrocortical response to threatening faces in major depressive disorder. *Depression and Anxiety*. 2010; 27:813–820. [PubMed: 20577985]
- Gehricke JG, Shapiro D. Reduced facial expression and social context in major depression: discrepancies between facial muscle activity and self-reported emotion. *Psychiatry Research*. 2000; 95(2):157–167. [http://doi.org/10.1016/S0165-1781\(00\)00168-2](http://doi.org/10.1016/S0165-1781(00)00168-2). [PubMed: 10963801]
- Gorman JM. Treatment of generalized anxiety disorder. *Journal of Clinical Psychiatry*. 2002
- Grasso DJ, Simons RF. Perceived parental support predicts enhanced late positive event-related brain potentials to parent faces. *Biological Psychology*. 2011; 86:26–30. <http://doi.org/doi:10.1016/j.biopsycho.2010.10.002>. [PubMed: 20946935]
- Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG. Emotional valence modulates brain functional abnormalities in depression: Evidence from a meta-analysis of fMRI studies. *Neuroscience & Biobehavioral Reviews*. 2012
- Hajcak G, MacNamara A, Olvet DM. Event-related potentials, emotion, and emotion regulation: An Integrative Review. *Developmental Neuropsychology*. 2010; 35:129–155. <http://doi.org/doi:10.1080/87565640903526504>. [PubMed: 20390599]
- Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. *The American Journal of Psychiatry*. 2012; 169(7):693–703. <http://doi.org/10.1176/appi.ajp.2012.11071105>. [PubMed: 22535198]
- Heller W. The puzzle of regional brain activity in depression and anxiety: The importance of subtypes and comorbidity. *Neuropsychological Perspectives on Affective and Anxiety Disorders*. 1998; 421
- Hilbert K, Lueken U, Beesdo-Baum K. Neural structures, functioning and connectivity in Generalized Anxiety Disorder and interaction with neuroendocrine systems: A systematic review. *Journal of Affective Disorders*. 2014; 158:114–126. <http://doi.org/10.1016/j.jad.2014.01.022>. [PubMed: 24655775]
- Kappenman ES, Farrens JL, Luck SJ, Proudfit GH. Behavioral and ERP measure attentional bias to threat in the dot-probe task: poor reliability and lack of correlation with anxiety. *Frontiers in Psychology*. 2014; 5:1368. <http://doi.org/10.3389/fpsyg.2014.01368>. [PubMed: 25538644]
- Kappenman, ES.; MacNamara, A.; Proudfit, GH. Electrocortical evidence for rapid allocation of attention to threat in the dot-probe task. *Social Cognitive and Affective Neuroscience*. 2014. <http://doi.org/10.1093/scan/nsu098>
- Kayser J, Bruder GE, Tenke CE, Stewart JE, Quitkin FM. Event-related potential (ERPs) to hemifield presentations of emotional stimuli: differences between depressed patient and healthy adults in P3 amplitude and asymmetry. *International Journal of Psychophysiology*. 2000; 36:211–236.
- Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Generalized anxiety disorder in women: a population-based twin study. *Archives of General Psychiatry*. 1992; 49:267–272. [PubMed: 1558460]
- Kerr N, Scott J, Phillips ML. Patterns of attentional deficits and emotional bias in bipo and major depressive disorder. *The British Journal of Clinical Psychology/the British Psychological Society*. 2005; 44(Pt 3):343–356. <http://doi.org/10.1348/014466505X57755>. [PubMed: 16238881]
- Kessler, RC.; Walters, EE.; Wittchen, HU. Epidemiology. In: Heimberg, RG.; Tu, CL.; Mennin, DS., editors. *Generalized anxiety disorder: advances in research and practice*. New York: Guilford Press; 2004. p. 50

- Kotov R, Perlman G, Gámez W, Watson D. The structure and short-term stability of the emotional disorders: A dimensional approach. *Psychological Medicine*. 2015; 8:1687–1698. [PubMed: 25499142]
- Krueger RF, Markon KE. Reinterpreting Comorbidity: A Model-Based Approach to Understanding and Classifying Psychopathology. *Annual Review of Clinical Psychology*. 2006; 2:111–133. <http://doi.org/10.1146/annurev.clinpsy.2.022305.095213>.
- Kujawa A, Hajcak G, Torpey D, Kim J, Klein DN. Electrocortical reactivity to emotional faces in young children and associations with maternal and paternal depression. *Journal of Child Psychology and Psychiatry*. 2012; 53:207–215. [PubMed: 21895650]
- Lawrence AE, Liverant GI, Rosellini AJ, Brown TA. Generalized anxiety disorder within the course of major depressive disorder: examining the utility of the DSM-IV hierarchy rule. *Depression and Anxiety*. 2009; 26(10):909–916. <http://doi.org/10.1002/da.20607>. [PubMed: 19798759]
- Lydiard, RB.; Monnier, J. Pharmacological treatment. In: Heimberg, RG.; Turk, CL.; Mennin, DS., editors. *Generalized anxiety disorder: advances in research and practice*. New York: Guilford Press; 2004. p. 351–382.
- MacNamara A, Hajcak G. Anxiety and spatial attention moderate the electrocortical response to aversive pictures. *Neuropsychologia*. 2009; 47:2975–2980. <http://doi.org/doi:10.1016/j.neuropsychologia.2009.06.026>. [PubMed: 19576234]
- MacNamara A, Hajcak G. Distinct electrocortical and behavioral evidence for increased attention to threat in Generalized Anxiety Disorder. *Depression and Anxiety*. 2010; 27:234–243. <http://doi.org/10.1002/da.20679>. [PubMed: 20196100]
- MacNamara A, Proudfit GH. Cognitive load and emotional processing in generalized anxiety disorder: Electrocortical evidence for increased distractibility. *Journal of Abnormal Psychology*. 2014; 123(3):557–565. <http://doi.org/10.1037/a0036997>. [PubMed: 24933276]
- Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. *Annu Rev Clin Psychol*. 2005; 1:167–195. [PubMed: 17716086]
- Mathews A, Ridgeway V, Williamson DA. Evidence for attention to threatening stimuli in depression. *Behaviour Research and Therapy*. 1996; 34:695–705. [PubMed: 8936752]
- Mennin DS, Heimberg RG, Fresco DM, Ritter MR. Is Generalized Anxiety Disorder an anxiety or mood disorder? Considering multiple factors as we ponder the fate of GAD. *Depression and Anxiety*. 2008; 25:289–299. [PubMed: 18412056]
- Mennin DS, McLaughlin KA, Flanagan TJ. Emotion regulation deficits in generalized anxiety disorder, social anxiety disorder, and their co-occurrence. *Journal of Anxiety Disorders*. 2009; 23(7):866–871. <http://doi.org/10.1016/j.janxdis.2009.04.006>. [PubMed: 19464142]
- Mochcovitch MD, da Rocha Freire RC, Garcia RF, Nardi AE. A systematic review of fMRI studies in generalized anxiety disorder: Evaluating its neural and cognitive basis. *Journal of Affective Disorders*. 2014; 167:336–342. <http://doi.org/10.1016/j.jad.2014.06.041>. [PubMed: 25020268]
- Moffitt TE, Harrington HL, Caspi A, Kim-Cohen J, Goldberg D, Gregory AM, Poulton R. Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Archives of General Psychiatry*. 2007; 64:651. [PubMed: 17548747]
- Mogg K, Bradley BP, Williams R. Attentional bias in anxiety and depression: The role of awareness. *British Journal of Clinical Psychology*. 1995; 34:17–36. [PubMed: 7757037]
- Mogg K, Bradley BP, Williams R, Mathews A. Subliminal processing of emotional information in anxiety and depression. *Journal of Abnormal Psychology*. 1993; 102:304–311. [PubMed: 8315143]
- Mogg K, Holmes A, Garner M, Bradley BP. Effects of threat cues on attentional shifting, disengagement and response slowing in anxious individuals. *Behaviour Research and Therapy*. 2008; 46:656–667. [PubMed: 18395185]
- Morris SE, Cuthbert BN. Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialogues Clin Neurosci*. 2012; 14(1):29–37. [PubMed: 22577302]
- Nelson, BD.; Perlman, G.; Hajcak, G.; Klein, DN.; Kotov, R. Familial risk for distress and fear disorders and emotional reactivity in adolescence: an event-related potential investigation; *Psychological Medicine*. 2015. p. 1–12. <http://doi.org/10.1017/S0033291715000471>

- Nesse RM. Is depression an adaptation? *Archives of General Psychiatry*. 2000; 57:14. [PubMed: 10632228]
- Proudfit GH, Bress JN, Foti D, Kujawa A, Klein DN. Depression and event-related potentials: emotional disengagement and reward insensitivity. *Current Opinion in Psychology*. 2015; 4:110–113. <http://doi.org/10.1016/j.copsyc.2014.12.018>. [PubMed: 26462292]
- Rinck M, Becker ES, Kellermann J, Roth WT. Selective attention in anxiety: Distraction and enhancement in visual search. *Depression and Anxiety*. 2003; 18:18–28. [PubMed: 12900949]
- Rivas-Vazquez RA. Antidepressants as first-line agents in the current pharmacotherapy of anxiety disorders. *Professional Psychology: Research and Practice*. 2001; 32:101–104.
- Rottenberg J, Gross JJ. When Emotion Goes Wrong: Realizing the Promise of Affective Science. *Clinical Psychology: Science and Practice*. 2006; 10(2):227–232. <http://doi.org/10.1093/clipsy.bpg012>.
- Rottenberg J, Gross JJ, Gotlib IH. Emotion context insensitivity in major depressive disorder. *Journal of Abnormal Psychology*. 2005; 114:627–639. [PubMed: 16351385]
- Rottenberg J, Kasch KL, Gross JJ, Gotlib IH. Sadness and amusement reactivity differentially predict concurrent and prospective functioning in major depressive disorder. *Emotion*. 2002; 2(2):135–146. <http://doi.org/10.1037/1528-3542.2.2.135>. [PubMed: 12899187]
- Roy MA, Neale MC, Pedersen NL, Mathe AA, Kendler KS. A twin study of generalized anxiety disorder and major depression. *Psychological Medicine*. 1995; 25:1037–1050. [PubMed: 8588001]
- Ruggero CJ, Kotov R, Watson D, Kilmer JN, Perlman G, Liu K. Beyond a single index of mania symptoms: Structure and validity of subdimensions. *Journal of Affective Disorders*. 2014; 161:8–15. <http://doi.org/10.1016/j.jad.2014.02.044>. [PubMed: 24751301]
- Sass SM, Heller W, Stewart JL, Sifton RL, Edgar JC, Fisher JE, Miller GA. Time course of attentional bias in anxiety: Emotion and gender specificity. *Psychophysiology*. 2009; 47:247–259. [PubMed: 19863758]
- Schmukle SC. Unreliability of the dot probe task. *European Journal of Personality*. 2005; 19:595–605.
- Schupp HT, Cuthbert BN, Bradley MM, Cacioppo JT, Ito T, Lang PJ. Affective picture processing: The late positive potential is modulated by motivational relevance. *Psychophysiology*. 2000; 37:257–261. <http://doi.org/doi:10.1111/1469-8986.3720257>. [PubMed: 10731776]
- Staugaard SR. Reliability of two versions of the dot-probe task using photographic faces. *Psychology Science Quarterly*. 2009; 51:339–350.
- Stockburger J, Schmälzle R, Flaisch T, Bublatzky F, Schupp HT. The impact of hunger on food cue processing: An event-related brain potential study. *Neuroimage*. 2009; 47:1819–1829. [PubMed: 19409497]
- Taylor-Clift A, Morris BH, Rottenberg J, Kovacs M. Emotion-modulated startle in anxiety disorders is blunted by co-morbid depressive episodes. *Psychological Medicine*. 2011; 41(01):129–139. <http://doi.org/10.1017/S003329171000036X>. [PubMed: 20230657]
- Teachman BA, Joormann J, Steinman SA, Gotlib IH. Automaticity in anxiety disorders and major depressive disorder. *Clinical Psychology Review*. 2012; 32(6):575–603. <http://doi.org/10.1016/j.cpr.2012.06.004>. [PubMed: 22858684]
- Vaidyanathan U, Patrick CJ, Cuthbert BN. Linking dimensional models of internalizing psychopathology to neurobiological systems: affect-modulated startle as an indicator of fear and distress disorders and affiliated traits. *Psychological Bulletin*. 2009; 135:909. [PubMed: 19883142]
- Vico C, Guerra P, Robles H, Vila J, Anllo-Vento L. Affective processing of loved faces: Contributions from peripheral and central electrophysiology. *Neuropsychologia*. 2010; 48:2894–2902. <http://doi.org/doi:10.1016/j.neuropsychologia.2010.05.031>. [PubMed: 20678982]
- Waechter S, Nelson AL, Wright C, Hyatt A, Oakman J. Measuring Attentional Bias to Threat: Reliability of Dot Probe and Eye Movement Indices. *Cognitive Therapy and Research*. 2013; 38(3):313–333. <http://doi.org/10.1007/s10608-013-9588-2>.
- Wang L, LaBar KS, Smoski M, Rosenthal MZ, Dolcos F, Lynch TR, et al. McCarthy G. Prefrontal mechanisms for executive control over emotional distraction are altered in major depression. *Psychiatry Research*. 2008; 163(2):143–155. <http://doi.org/10.1016/j.psychres.2007.10.004>. [PubMed: 18455373]

- Watson D. Rethinking the mood and anxiety disorders: A quantitative hierarchical model for DSM-V. *Journal of Abnormal Psychology*. 2005; 114:522–536. [PubMed: 16351375]
- Watson D. Differentiating the mood and anxiety disorders: a quadripartite model. *Annual Review of Clinical Psychology*. 2009; 5:221–247. <http://doi.org/10.1146/annurev.clinpsy.032408.153510>.
- Watson D, Clark LA, Chmielewski M, Kotov R. The Value of Suppressor Effects in Explicating the Construct Validity of Symptom Measures. *Psychological Assessment*. 2013; 25(3):929–941. <http://doi.org/10.1037/a0032781>. [PubMed: 23795886]
- Watson D, O'Hara MW, Naragon-Gainey K, Koffel E, Chmielewski M, Kotov R, et al. Ruggero CJ. Development and Validation of New Anxiety and Bipolar Symptom Scales for an Expanded Version of the IDAS (the IDAS-II). *Assessment*. 2012; 19(4):399–420. <http://doi.org/10.1177/1073191112449857>. [PubMed: 22822173]
- Weinberg A, Hajcak G. Electrocortical evidence for vigilance-avoidance in Generalized Anxiety Disorder. *Psychophysiology*. 2011; 48:842–851. [PubMed: 21073479]
- Weinberg A, Klein DN, Hajcak G. Increased error-related brain activity distinguishes generalized anxiety disorder with and without comorbid major depressive disorder. *Journal of Abnormal Psychology*. 2012; 121:885–896. <http://doi.org/doi:10.1037/a0028270>. [PubMed: 22564180]
- Weinberg, A.; Venables, NC.; Proudfit, GH.; Patrick, CJ. Heritability of the neural response to emotional pictures: evidence from ERPs in an adult twin sample. *Social Cognitive and Affective Neuroscience*. 2014. <http://doi.org/10.1093/scan/nsu059>
- Wexler BE, Levenson L, Warrenburg S, Price LH. Decreased perceptual sensitivity to emotion-evoking stimuli in depression. *Psychiatry Research*. 1994; 51(2):127–138. [PubMed: 8022947]
- Williams, JMG.; Watts, FN.; MacLeod, C.; Mathews, A. *Cognitive psychology and emotional disorders*. New York: John Wiley & Sons; 1988.
- Wright CI, Fischer H, Whalen PJ, McInerney SC, Shin LM, Rauch SL. Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *Neuroreport*. 2001; 12:379–383. [PubMed: 11209954]
- Zimmerman M, Chelminski I. Generalized anxiety disorder in patients with major depression: is DSM-IV's hierarchy correct? *The American Journal of Psychiatry*. 2003; 160(3):504–512. [PubMed: 12611832]

Fig 1.

A sample trial from the task. Participants viewed a pair of identical neutral or unpleasant images above and below the center of the screen. Following picture offset, a target appeared in place of one of the previously presented images; participants indicated whether the target was a circle or a square.

Fig 2.

Bar graphs depicting mean residual values representing variance unique to unpleasant pictures after controlling for the response to neutral pictures, shown separately for RT (top) and LPP (bottom): individuals without a diagnosis of GAD or MDD (healthy adults, “HA”), individuals with a diagnosis of GAD but not MDD (“GAD”), individuals with MDD but not GAD (“MDD”) and individuals with GAD and MDD (“Comorbid”). Error bars represent standard error of the mean. (GAD diagnoses made using the DSM-IV hierarchical criterion).

Fig 3.

Grand-average ERP waveforms at central-parietal pooling, CP1, CP2, Cz and Pz for each condition as well as topographic maps illustrating the difference between unpleasant minus neutral pictures between 400-1000 ms after pictures onset, presented separately for participants with varying levels of IMAS Generalized Anxiety and IMAS Depression: low anxiety, low depression ($n = 10$, top left); high anxiety, low depression ($n = 10$, top right); low anxiety, high depression ($n = 10$, bottom left) and high anxiety, high depression ($n = 10$, bottom right). Groups were created for illustrative purposes only.

Table 1

Sample characteristics.

	Healthy Adults (<i>n</i> = 23)		MDD (<i>n</i> = 36)		GAD (<i>n</i> = 22)		Comorbid (<i>n</i> = 30)		All Patients (<i>n</i> = 88)		Overall (<i>n</i> = 111)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Gender												
Female	13	56.5	22	61.1	16	72.7	23	23.3	61	69.3	74	66.7
Male	10	43.5	14	38.9	6	27.3	7	76.7	27	30.7	37	33.3
Ethnicity												
Caucasian	20	87.0	28	80.0	19	86.4	25	83.3	72	81.8	92	82.9
Other	3	13.0	7	19.4	3	13.6	5	16.7	15	17.0	18	16.2
Unknown	0	0	1	2.8	0	0	0	0	1	1.1	1	.9
Diagnoses												
MDD <i>a.b.d.e.g</i>	0	0	36	100.0	0	0	30	100.0	66	75.0	66	59.4
GAD <i>a.c.d.e.f</i>	0	0	0	0	22	100.0	30	100.0	52	59.1	52	46.8
Specific Phobia <i>a.b.c.d</i>	1	4.3	14	38.9	11	50.0	11	36.7	36	40.9	37	33.3
Panic <i>a.b.d.e</i>	0	0	14	38.9	3	13.6	11	36.7	28	31.8	28	25.2
Social Phobia <i>a.b.c.d</i>	0	0	8	22.2	6	27.3	7	23.3	21	23.9	21	18.9
Agoraphobia <i>a.b.d</i>	0	0	9	25.0	2	9.1	8	26.7	19	21.6	19	17.1
Substance use <i>a.b.c.d</i>	0	0	7	19.4	4	18.2	7	23.3	18	20.4	18	16.2
PTSD <i>a.b</i>	0	0	8	22.2	2	9.1	4	13.3	14	15.9	14	12.6
OCD	0	0	3	8.3	3	13.6	4	13.3	10	11.4	10	9.0
Dysthymia	0	0	3	8.3	3	13.6	3	10.0	9	10.2	9	8.1
Medication												
Antidepressant <i>a.b.c.d</i>	0	0	24	66.7	14	63.6	26	86.7	64	72.7	64	57.6
Anxiolytic <i>a.b.c.d</i>	0	0	18	50.0	8	36.4	18	60.0	44	50.0	44	39.6
Antipsychotic <i>a.b.c.d</i>	0	0	12	33.3	7	31.8	10	33.3	29	33.0	29	26.1
Mood stabilizer <i>a.d</i>	0	0	5	13.9	2	9.1	9	30.0	16	18.2	16	14.4

	Healthy Adults (<i>n</i> = 23)		MDD (<i>n</i> = 36)		GAD (<i>n</i> = 22)		Comorbid (<i>n</i> = 30)		All Patients (<i>n</i> = 88)		Overall (<i>n</i> = 111)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Hypnotic <i>a,d</i>	0	0	6	16.7	3	13.6	6	20.0	15	17.0	15	13.5
Stimulant <i>c</i>	0	0	2	5.6	3	13.6	4	13.3	9	10.2	9	8.1
Other psychiatric <i>c,e</i>	0	0	0	0	3	13.6	2	6.7	5	5.7	5	4.5
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age <i>a,b,c,d</i>	56.8	8.5	41.4	11.7	38.1	14.3	41.4	13.4	40.6	12.9	44.0	13.8
IMAS Depression <i>a,b,c,d,e,f,g</i>	4.0	6.5	61.4	12.6	34.1	17.4	68.8	9.6	57.1	18.8	46.1	27.5
IMAS Generalized Anxiety <i>a,b,c,d,e,f,g</i>	1.5	2.5	17.3	4.3	11.0	5.7	20.1	3.3	16.7	5.6	13.6	8.0

Significant between-groups differences (*p* < .05, Chi square, Fisher's Exact test or independent *t*-test) are indicated as follows:

^aHealthy Adults (HA) vs. All Patients;

^bHA vs. major depressive disorder (MDD);

^cHA vs. generalized anxiety disorder (GAD);

^dHA vs. Comorbid;

^eMDD vs. GAD;

^fMDD vs. Comorbid;

^gGAD vs. Comorbid. GAD diagnoses made using the DSM-IV hierarchical rule.