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ORIGINAL ARTICLE

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 generalized anxiety disorder (GAD) and major depressive disorder (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 GAD or 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 ΔLPP. When controlling for MDD diagnosis/dimension, both the diagnosis and dimension of GAD were associated with *increased* ΔLPP. Both MDD and GAD dimensions, but not diagnoses, were associated with increased ΔRT to targets that followed emotional pictures. Therefore, MDD and GAD have distinguishable and opposing features evident in neural measures of emotion processing.

Keywords GAD · MDD · ERP · Late positive potential · LPP · IAPS · Emotional context insensitivity · RDoC · IMAS · Transdiagnostic

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Introduction

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 et al. 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 et al. 1992; Roy et al. 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 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 et al. 2008), including indications of unique neurochemical (Lydiard and Monnier 2004) and psychological (e.g., Chelminski and Zimmerman 2003; Dugas et al. 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 et al. 1998; Clark and 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 et al. 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 et al. 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 and MacLeod 2005; Teachman et al. 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 (Bradley et al. 1997; Mogg et al. 1995). On the other hand, however, Mathews et al. (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 and 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 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 and Hajcak 2010; Rinck et al. 2003) and MDD (Wang et al. 2008). Using the emotional Stroop, in which the emotional nature of words is irrelevant to the task, Mogg et al. (1993) found that individuals with GAD had slower reaction times (RTs) for unpleasant words. This effect was not evident among participants with comorbid depression (Bradley et al. 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 and MacLeod 2005). Indeed, several studies suggest that GAD (Hilbert et al. 2014; Mennin et al. 2009) and MDD (Groenewold et al. 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 et al. 2005).

Substantial evidence supports the ECI model of depression (e.g., for a review, see Bylsma et al. 2007). For instance, individuals with MDD report less subjectively experienced affect when viewing sad or amusing film clips (Rottenberg et al. 2005; Rottenberg et al. 2002). MDD has also been associated with reduced emotional modulation of the startle reflex (Dichter and Tomarken 2008; Dichter et al. 2004; Taylor-Clift et al. 2011) and with decreased electromyographic facial responding when viewing emotional pictures as compared to healthy adults (HAs; Wexler et al. 1994) and patients with other disorders (Gehricke and Shapiro 2000). Of the studies described above, only two ensured that depressed participants were free from comorbid GAD (Gehricke and 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 et al. (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 and 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 et al. 2000; Dillon et al. 2006; Foti et al. 2009; Schupp et al. 2000). Functionally, the LPP is believed to reflect increased and elaborated attention to stimuli that have been deemed motivationally salient (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 et al. 2009) and to personally salient stimuli such as photographs of one's own relatives or loved ones (Grasso and Simons 2011; Vico et al. 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 and Proudfit 2014).

Work utilizing the LPP has tended to support the ECI view of depression (for a review, see Proudfit et al. 2015). For instance, Foti et al. (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 et al. (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 et al. 2012; see also Nelson et al. 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 (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 and Watson 1991; Krueger and 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 and 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 significant psychiatric diagnosis. Because transdiagnostic dimensions might relate more directly to underlying emotional brain circuits (Cuthbert 2014; Vaidyanathan et al. 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 et al. 2014b), 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 et al. 2014b). We also expected that GAD (diagnosis and dimension) would be associated with increased LPPs to unpleasant versus neutral pictures (MacNamara

and Hajcak 2010; MacNamara and 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 and 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 difficulty. 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 GAD or MDD. Diagnoses were made according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV (SCID; First et al. 2007), which assesses for the presence of GAD in the past 6 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 three 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 et al. 2009; Zimmerman and 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 images.[1] 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 et al. 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 et al. 2013). We used the IMAS Generalized Anxiety and IMAS Depression scales in order to assess GAD- and MDD-related symptomatology continuously

[1] IAPS 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.

Table 1 Sample characteristics

	Healthy adults ($n = 23$)		MDD ($n = 36$)		GAD ($n = 22$)		Comorbid ($n = 30$)		All patients ($n = 88$)		Overall ($n = 111$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
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[a,b,d,e,g]	0	0	36	100.0	0	0	30	100.0	66	75.0	66	59.4
GAD[a,c,d,e,f]	0	0	0	0	22	100.0	30	100.0	52	59.1	52	46.8
Specific Phobia[a,b,c,d]	1	4.3	14	38.9	11	50.0	11	36.7	36	40.9	37	33.3
Panic[a,b,d,e]	0	0	14	38.9	3	13.6	11	36.7	28	31.8	28	25.2
Social Phobia[a,b,c,d]	0	0	8	22.2	6	27.3	7	23.3	21	23.9	21	18.9
Agoraphobia[a,b,d]	0	0	9	25.0	2	9.1	8	26.7	19	21.6	19	17.1
Substance use[a,b,c,d]	0	0	7	19.4	4	18.2	7	23.3	18	20.4	18	16.2
PTSD[a,b]	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[a,b,c,d]	0	0	24	66.7	14	63.6	26	86.7	64	72.7	64	57.6
Anxiolytic[a,b,c,d]	0	0	18	50.0	8	36.4	18	60.0	44	50.0	44	39.6
Antipsychotic[a,b,c,d]	0	0	12	33.3	7	31.8	10	33.3	29	33.0	29	26.1
Mood stabilizer[a,d]	0	0	5	13.9	2	9.1	9	30.0	16	18.2	16	14.4
Hypnotic[a,d]	0	0	6	16.7	3	13.6	6	20.0	15	17.0	15	13.5
Stimulant[c]	0	0	2	5.6	3	13.6	4	13.3	9	10.2	9	8.1
Other psychiatric[c,e]	0	0	0	0	3	13.6	2	6.7	5	5.7	5	4.5

	Healthy adults ($n = 23$)		MDD ($n = 36$)		GAD ($n = 22$)		Comorbid ($n = 30$)		All patients ($n = 88$)		Overall ($n = 111$)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age[a,b,c,d]	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[a,b,c,d,e,f,g]	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[a,b,c,d,e,f,g]	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: [a] Healthy adults (HA) versus all patients; [b] HA versus major depressive disorder (MDD); [c] HA versus generalized anxiety disorder (GAD); [d] HA versus comorbid; [e] MDD versus GAD; [f] MDD versus Comorbid; [g] GAD versus Comorbid. GAD diagnoses made using the DSM-IV hierarchical rule

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-h 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 Fig. 1. Stimuli were presented on a black background using an LCD monitor

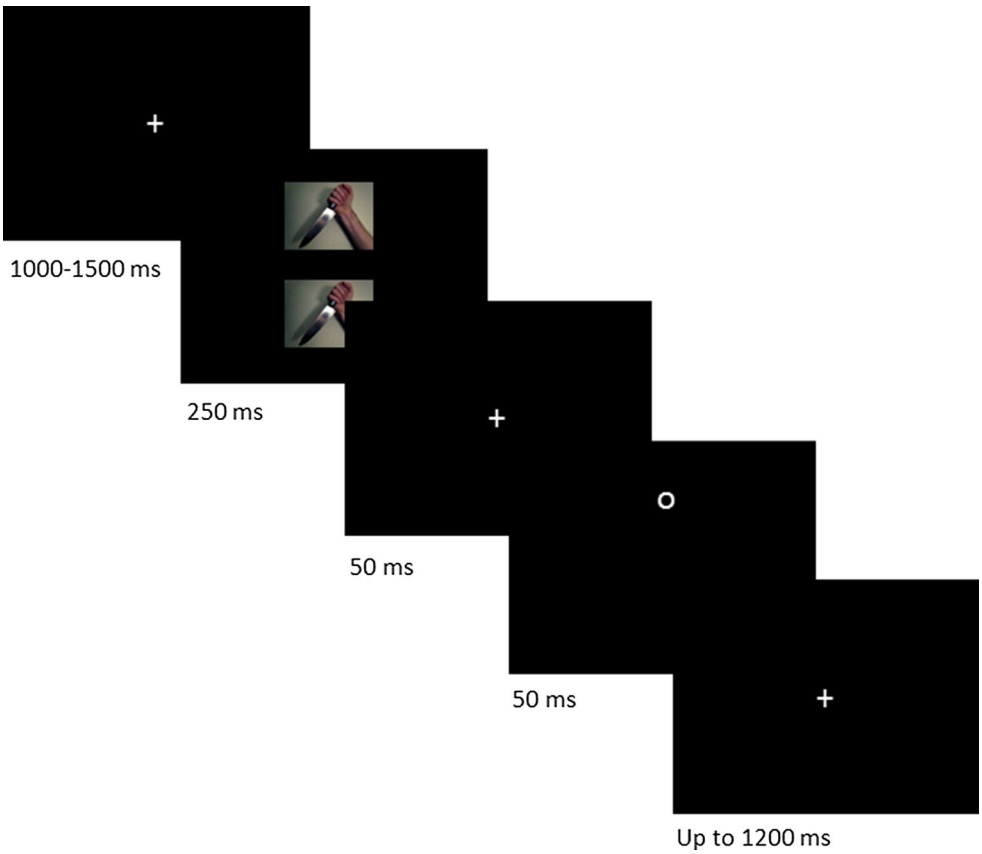

Fig. 1 A sample trial from the task. Participants viewed a pair of identical neutral or unpleasant images *above* and *below* the *center* of the screen. Following picture offset, a target appeared in place of one of the previously presented images; participants indicated whether the target was a *circle* or a *square*

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 × .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 1200 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 1000–1500 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 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 .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 et al. (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 .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 1200 ms (i.e., until 1000 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 to 1000 ms after picture onset, in line with prior work (e.g., MacNamara and 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 and 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 et al. 2015). 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 ΔRT and ΔLPP.

We used linear regression to examine associations of ΔRT and ΔLPP with MDD and GAD diagnoses, as well as associations between each of ΔRT and ΔLPP and IMAS Depression, IMAS Generalized Anxiety.[2] Next, both diagnoses and symptoms were entered as predictors in the same regression, to determine whether variance in ΔRT and ΔLPP 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 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, $M = 2.21$ μv, $SD = 2.87$; unpleasant pictures, $M = 3.04$ μv, $SD = 2.85$]. All subsequent analyses were performed using ΔRT and ΔLPP.

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

GAD and MDD Diagnoses

To examine relationships between GAD, MDD, ΔRT and ΔLPP, 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 ΔRT. Results showed that GAD alone was not associated with ΔRT [$R^2 = .00$, $F(1, 109) = .23$, $p = .64$; $\beta = .04$]; 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 ΔRT, the association with GAD was still non-significant ($\beta = .05$, $p = .59$). When controlling for the relationship between GAD diagnosis and ΔRT, the effect of MDD also remained non-significant ($\beta = .17$, $p = .07$). 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 ΔRT [$R^2 = .00$, $F(1, 109) = .58$, $p = .45$; $\beta = .07$]. 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 ΔLPP showed that separately, GAD diagnosis was not associated with ΔLPP [$R^2 = .01$, $F(1, 109) = .61$, $p = .44$; $\beta = .08$]; MDD, on the other hand, was associated with attenuated ΔLPP [$R^2 = .05$, $F(1, 109) = 5.49$, $p = .02$; $\beta = -.22$; Fig. 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 ΔLPP ($\beta = -.22$, $p = .02$). When ignoring the DSM-IV hierarchical criterion (APA 2000), GAD was still not associated with ΔLPP [$R^2 = .03$, $F(1, 109) = 2.98$, $p = .09$; $\beta = .16$]. 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 ΔLPP ($\beta = .19$, $p = .046$) and MDD was still associated with reduced ΔLPP ($\beta = -.24$, $p = .01$).

GAD and MDD Symptomatology

To examine relationships between continuous measures of GAD and MDD symptomatology and each of ΔRT and ΔLPP, we performed a series of linear regressions. First, we entered IMAS Generalized Anxiety and IMAS Depression into separate linear regressions predicting ΔRT. Results showed that higher IMAS Generalized Anxiety scores were associated with greater ΔRT—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 ΔRT [$R^2 = .04$, $F(1, 109) = 4.05$, $p = .05$; $\beta = .19$]. 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 ΔLPP, results showed that IMAS Generalized Anxiety was not associated with ΔLPP [$R^2 = .01$, $F(1, 109) = .86$, $p = .36$; $\beta = -.09$]; however, higher IMAS Depression scores were associated with reduced ΔLPP [$R^2 = .04$, $F(1, 109) = 5.01$, $p = .03$; $\beta = -.21$]. When IMAS Generalized Anxiety and IMAS Depression were entered into the model simultaneously, both IMAS scales were associated with ΔLPP [$R^2 = .09$, $F(2, 108) = 5.17$, $p = .007$]. ERP waveforms and topographic maps depicting these effects are presented in Fig. 3. When controlling for the association of depressive symptoms with the LPP, GAD symptoms were associated with increased ΔLPP ($\beta = .45$, $p = .02$).

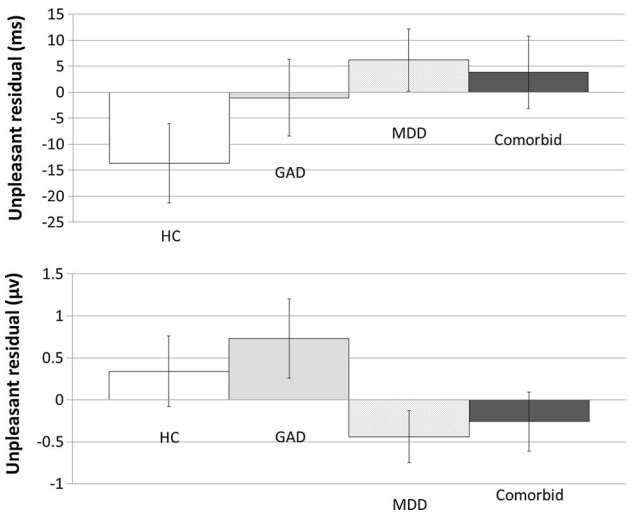

Fig. 2 *Bar graphs* depicting mean residual values representing variance unique to unpleasant pictures after controlling for the response to neutral pictures, shown separately for RT (*top*) and LPP (*bottom*): individuals without a diagnosis of GAD or MDD (healthy adults, "HA"), individuals with a diagnosis 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)

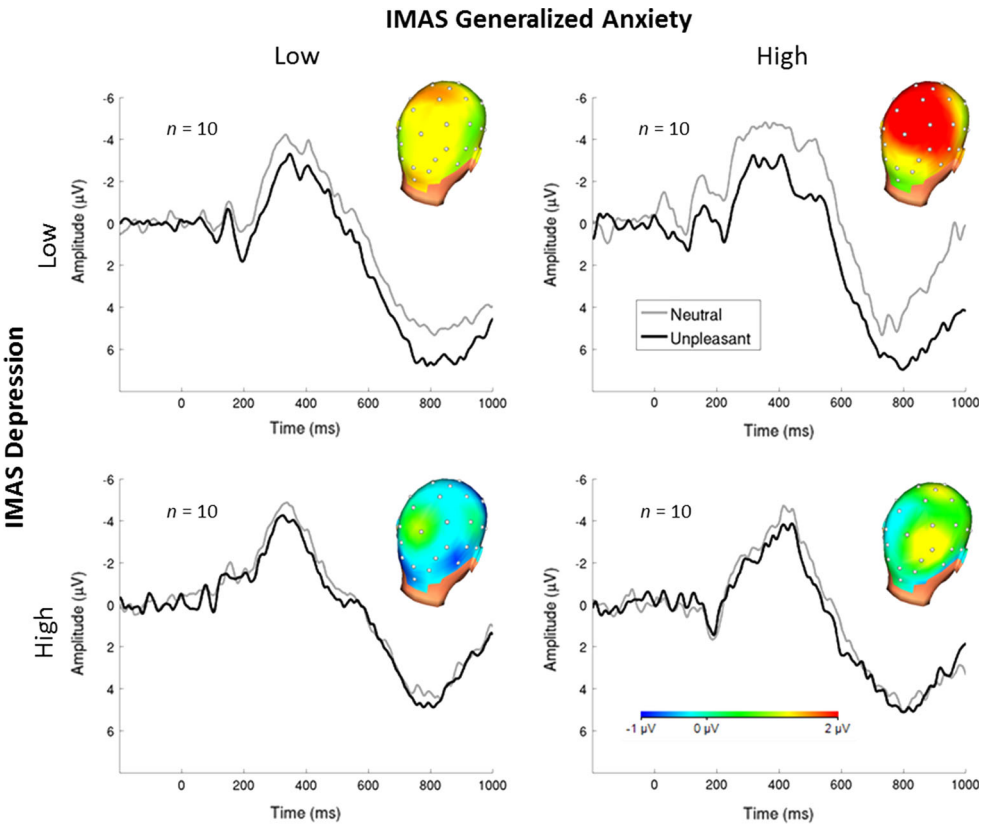

Fig. 3 Grand-average ERP waveforms at central-parietal pooling, CP1, CP2, Cz and Pz for each condition as well as topographic maps illustrating the difference between unpleasant minus neutral pictures between 400 and 1000 ms after pictures onset, presented separately for participants with varying levels 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

When controlling for the association between GAD symptoms and the LPP, depressive symptoms continued to be associated with reduced ΔLPP ($\beta = -.61$, $p = .003$).

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 ΔRT and (b) a linear regression predicting ΔLPP. These analyses allowed us to determine whether a dimensional or categorical approach to description of these conditions was better at accounting for variance in ΔRT and ΔLPP. For ΔRT, 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 ΔLPP, the overall model was significant [$R^2 = .10$, $F(4, 106) = 3.03$, $p = .02$]. Furthermore, IMAS Generalized Anxiety was associated with increased ΔLPP ($\beta = .45$, $p = .03$) and IMAS Depression was associated with reduced ΔLPP ($\beta = -.51$, $p = .03$). 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) ΔRT and (b) ΔLPP. For ΔRT, 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 ΔLPP, the overall model was significant [$R^2 = .14$, $F(4, 106) = 4.32$, $p = .003$]. IMAS Generalized Anxiety was no longer associated with increased ΔLPP ($\beta = .38$, $p = .06$), however IMAS Depression was still associated with reduced ΔLPP ($\beta = -.61$, $p = .01$). A diagnosis of GAD was associated with increased ΔLPP ($\beta = .24$, $p = .03$); the association with MDD was still non-significant ($\beta = -.03$, $p = .87$).

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 et al. 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 et al. 2007; Wright et al. 2001), and the LPP, which measures elaborated stimulus processing and is relatively insensitive to the effects of habituation (Codispoti et al. 2007; Hajcak et al. 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 and 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 and 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 and 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 s). 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 stimuli,[3] 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 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 et al. 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 and 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 and Schatzberg 2011; Heller and Nitschke 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 and Chelminski 2003). In the current study, a diagnosis of GAD

[3] Indeed, Weinberg and Hajcak (2011) found evidence of an increased early ERP (the P1) to unpleasant stimuli in 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 et al. 2001; Chen et al. 2013; Kerr et al. 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 et al. 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 et al. 2014b; Schmukle 2005; Staugaard 2009; Waechter et al. 2013); using the same task, however, ERPs are reliable (Kappenman et al. 2014a, b). 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 et al. 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 was 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 and 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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Compliance with Ethical Standards

Conflict of Interest Annmarie MacNamara, Roman Kotov and Greg Hajcak declare that they have no conflict of interest.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (national and institutional). Informed consent was obtained from all individual subjects participating in the study.

Animal Rights No animal studies were carried out by the authors for this paper.

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