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Dissociating Disorders of Depression, Anxiety, and their Comorbidity with Measures of Emotional Processing: A Joint Analysis of Visual Brain Potentials and Auditory Perceptual Asymmetries

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Highlights

- Studied emotion processing differences in depression, anxiety and their comorbidity
- Jointly analyzed visual brain potentials (P3) and auditory perceptual asymmetries
- Used logistic regression to predict history of each mood disorder category
- Depression linked to reduced and heightened emotional responsivity across measures
- Comorbidity separately linked to reduced emotional responsivity of either measure

Abstract (150 words)

In a multigenerational study of families at risk for depression, individuals with a lifetime history of depression had: 1) abnormal perceptual asymmetry (PA; smaller left ear/right hemisphere [RH] advantage) in a dichotic emotion recognition task, and 2) reduced RH late positive potential ($P3_{RH}$) during an emotional hemifield task. We used standardized difference scores for processing auditory (PA sad-neutral) and visual ($P3_{RH}$ negative-neutral) stimuli for 112 participants (52 men) in a logistic regression to predict history of depression, anxiety or comorbidity of both. Whereas comorbidity was separately predicted by reduced PA (OR=0.527, p=.042) or $P3_{RH}$ (OR=0.457, p=.013) alone, an interaction between PA and $P3_{RH}$ (OR=2.499, p=.011) predicted depressive disorder. Follow-up analyses revealed increased probability of depression at low (lack of emotional differentiation) and high (heightened reactivity to negative stimuli) levels of both predictors. Findings suggest that reduced or heightened right-lateralized emotional responsivity to negative stimuli may be uniquely associated with depression.

Keywords: depression, anxiety, emotional lateralization, visual ERPs, dichotic listening

Emotion processing is essential for survival, serving as the basis for effective approach or defensive responses to changes in the environment (e.g., Bradley, 2009). As emotion drives motivation, being able to recognize and differentiate emotional stimuli is crucial for healthy cognitive and behavioral functioning. Deficits in affective and cognitive processing are present in patients with various mood disorders, leading to their impaired psychosocial functioning and symptom presentation (Weightman, Air & Baune, 2014; Knight & Baune, 2017; Moratti et al., 2008). Thus, further understanding neural mechanisms associated with emotional abnormalities may be beneficial to the differential diagnosis of mood disorders and treatment of emotion processing dysfunctions.

Comparing Emotion Abnormalities across Mood Disorders

Robust differences between patients having a depressive disorder and healthy controls have been found in electrophysiological measures, such as event related potentials (ERP), where depressed patients exhibited blunted cortical reactivity in electrophysiological responses to emotional stimuli (e.g., Deldin et al., 2000; Kayser et al., 2000). Individuals with a lifetime history of depression had a smaller emotional effect in P3 source, an ERP subcomponent of the late positive potential (LPP), to unpleasant versus neutral stimuli than healthy individuals (Kayser et al., 2017). Modulations of LPP amplitude are regarded as neurophysiological correlates of enhanced attention to motivational significant stimuli (e.g., Polich, 2007; Keil et al., 2002). In contrast, patients with generalized anxiety disorder (GAD) showed an *increased* modulation of LPP in response to negative than neutral pictures (MacNamara, Kotov & Hajcak, 2016). The LPP is a broader, long-lasting ERP that incorporates P3 as a subcomponent (Kayser et al., 2016) and is associated with emotional arousal (for reviews, see Hajcak et al., 2012; Olofsson et al., 2008). Furthermore, we found differences in ERPs among patients having depression, anxiety or comorbidity of these disorders during tonal and phonetic oddball tasks (Bruder et al., 2002). A late P3 subcomponent was larger in patients with comorbid disorders compared with patients having either disorder alone or healthy controls, and a task-dependent hemispheric asymmetry of N2-P3 complex was largest in patients having a depressive disorder alone and smallest in patients having an anxiety disorder alone (Bruder et al., 2002). Although this study used cognitive ERPs, it is likely that ERPs to emotional stimuli may not only reveal diagnostic group differences but also differences in right-lateralized processing. These electrophysiological findings strongly suggest differences in emotional dysregulation in depression, anxiety, and their comorbidity.

Emotional Lateralization: The Focus on Right Hemispheric Activity

Reduced emotional responsivity in depression is associated with a hypoactivation of the right temporoparietal cortex, which is critically involved in detection of stimulus significance and emotional modulation of attention (e.g., Bruder, Stewart & McGrath, 2017; Heller & Nitschke, 1997; Kayser et al., 2000, 2016). However, individuals with comorbid depression and anxiety had greater right-lateralized P3 for emotionally pleasant words compared to those with depression only (Sass et al., 2014). This suggests that right-hemispheric activity may be influenced by anxiety-related attentional bias and subsequent cognitive processing of emotional stimuli (Fisher et al., 2010), although any lateralized effects may also be influenced by the semantic or linguistic properties of verbal stimuli. The effects of internalizing disorders on emotion processing are also evidenced by behavioral measures of hemispheric asymmetry. In dichotic listening tasks with emotional stimuli, healthy adults showed a left ear advantage (LEA), representing right hemisphere dominance for prosodic perception (Bryden & MacRae, 1989; Frühholz et al., 2016; Voyer et al., 2009), whereas individuals with a lifetime diagnosis of depression had reduced LEA (Bruder et al., 2016). This perceptual asymmetry (PA) is also evident in individuals with comorbid depression and anxiety disorders, who had a larger LEA for perceiving dichotic complex tones compared to those with a depression disorder alone (Bruder et al., 1999). Thus, evidence points to the right hemisphere's role in emotion processing, with the extent of hypoactivation dependent on the type and comorbidity of internalizing disorder.

Different Levels of Measurement and Sensory Domains

Previously used electrophysiological and behavioral tasks, in particular the emotional hemifield task (Kayser et al., 1997) and dichotic emotion recognition task (Bryden & MacRae,

1989), are sensitive to right-hemispheric emotion processing differences between healthy individuals and those with internalizing disorders. For the emotional hemifield task, individuals with a lifetime diagnosis of depression or anxiety exhibited a reduced emotional P3 effect (Kayser et al., 2017). Correspondingly, for the dichotic emotional recognition task, PA for the sad emotion condition was significantly smaller for participants with a lifetime depression diagnosis than those without depression (Bruder et al., 2016). Additionally, there was no difference in PA when comparing individuals with and without a history of anxiety disorder. These results suggest that P3 and PA may differentiate between individuals with an internalizing disorder and those without one. Whereas P3 directly reflects cortical responsivity to emotional stimuli, targeting both early and later stages of emotion processing, PA is a summation of multiple affective and cognitive processes cumulating in single behavioral metric. A *combined* analysis of these electrophysiological and behavioral measures will allow us to examine various stages of emotion processing in relation to specific disorders along the depression-anxiety spectrum.

Aside from combining these electrophysiological and behavioral measures, the ERP and dichotic tasks also probe visual and auditory modalities of emotion processing, reflecting the fact that everyday life involves multimodal perception and interpretation of stimuli. No effort has yet been made to directly compare the right-hemispheric emotion processing abnormalities in these two tasks. As processing in one sensory modality can affect information processing in another modality (Gerdes, Wieser & Alpers, 2014), it is crucial to identify differences in both visual and auditory emotional dysregulation in depression, anxiety, and their comorbidity. A deeper understanding of emotion processing will help further the identification of efficacious treatment options for internalizing disorders; however, to the best of our knowledge, no prior report has

jointly examined emotional processing in two sensory domains as it relates to anxiety, depression and comorbidity of these disorders within the same study.

Present Study

The aim of the present study was to identify differences between individuals diagnosed with depression, anxiety, or comorbid depression and anxiety, by building on previous work regarding right-hemisphere emotion processing abnormalities in affective disorders in different sensory domains and levels of measurement (Bruder et al., 2017; Deldin et al., 2000; Kayser et al., 2000; Moratti et al., 2008). Furthermore, by using diagnosis as the dependent variable in a new multinomial logistic regression, we sought to examine the probability of correctly predicting lifetime history of depression, anxiety, or comorbidity when combining visual ERP and auditory PA measures of emotional processing as predictors. We hypothesized that individuals with reduced P3 and PA are predicted to have a higher probability of a lifetime depressive disorder. Hypotheses concerning prediction of anxiety and comorbid disorders are uncertain because of inconsistent ERP and PA findings for these disorders. Notwithstanding, the hope was differentiation of depression, anxiety and their comorbidity would further our understanding of emotion processing deficits in these mood disorders.

Method

Participants

The sample consisted of 112 participants between 13 and 59 years of age (see Table 1 for demographics). Participants were selected only if they were included in both of two prior reports that focused on: 1) ERP components during an emotional hemifield paradigm (Kayser et al., 2017; $N = 127$), and 2) auditory perceptual asymmetry during a dichotic listening test of

emotional processing (Bruder et al., 2016; *N* = 128). All participants were right-handed (Oldfield, 1971), without hearing impairment (standard audiogram), Caucasian, and from the New Haven area (Connecticut, US) who had been enrolled in a longitudinal, multigenerational study of families at high and low risk for depression (Weissman et al., 1997, 2005, 2006). In the original wave of the study, probands with moderate to severe depression were recruited from outpatient clinics, with demographically matched control participants with no psychiatric history also recruited from the same community. All participants in this sample are the children and grandchildren of the participants from the original wave – descendants from the depressed probands were classified as high family risk for depression, while descendants from the healthy control participants were classified as low family risk for depression. All participants were interviewed though the years (i.e., wave 1 to 6) using age-appropriate versions of the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L; Endicott & Spitzer, 1978) to make depression, anxiety, and comorbid *lifetime* diagnoses (i.e., whether or not participants had depression and/or anxiety since the last clinical interview, allowing to assess their lifetime clinical diagnosis before EEG and dichotic listening testing). Participants with no prior depression and/or anxiety diagnoses were categorized in the "none" group. Diagnoses were made with a best-estimate procedure by experienced clinicians (either psychiatrists or Ph.D. psychologists) using all available information from assessments at prior waves of the longitudinal study. Clinicians determining these best-estimate diagnoses were not involved in the interviewing and were blind to the clinical status of previous generations. The 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) and 14-item Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959) were also administered to participants aged 18 and older to assess *current* depression and anxiety severity at the time of testing. EEG and dichotic listening tests

were performed at the Psychophysiology Laboratory at New York State Psychiatric Institute (NYSPI). All procedures were approved by the institutional review boards at Yale University and at Columbia University/NYSPI. All participants gave written informed consent (≥ 18 years) or provided written assent (< 18 years; written informed consent from parents). The sample was characterized by a wide range in age due to sampling and study design of this multigenerational study. We intentionally opted not to restrict the age range because of statistical power considerations and because of prior studies showing moderate to strong stability for the ERP measures of interest, suggesting that the P3 is stable across development (Kujawa et al., 2013; Pegg et al., 2019). Not surprisingly, however, subjects under 18 were disproportionately in the "none" group, likely due to the limited amount of time to develop any of these disorders, although the occurrence of a first depressive episode peaks from 15 to 18 years of age (Hankin et al., 1998). Thus, we also repeated all analyses for an adult-only (≥ 18 years, n = 95) subset of our sample. Given that there were few and only minor differences compared to the result reported below for the full sample, these additional analyses are detailed in the Supplementary Material.

Table 1. Crosstabulation of diagnosis with sex and familial risk for depression, and corresponding means (±SD) of age and clinical variables.

Diagnosis	*N*	Sex		Family Risk[a]		Age	HDRS[b]	HARS[c]
		M	F	High	Low	[min, max]	(*n* = 92)	(*n* = 90)
Depression only	19	6	13	10	9	36.5 ± 14.2 [15, 59]	2.3 ± 3.7	1.6 ± 3.1
Anxiety only	28	10	18	12	16	29.3 ± 11.3 [15, 49]	1.5 ± 2.8	1.6 ± 2.4
Comorbidity	34	15	19	28	6	40.0 ± 12.0 [16, 59]	3.8 ± 6.4	4.5 ± 7.0
None	31	21	10	14	17	26.5 ± 14.2 [13, 56]	2.0 ± 3.9	0.9 ± 2.1
Total	112	52	60	67	45	33.1 ± 13.9	2.5 ± 4.7	2.4 ± 4.7

Note. [a]Family Risk refers to whether the individual was a descendant of a Generation 1 proband (i.e., parent or grandparent) originally diagnosed with depression. [b]HDRS: Hamilton Depression Rating Scale (Hamilton, 1960). [c]HARS: Hamilton Anxiety Rating Scale (Hamilton, 1959). HDRS (*n* = 92) and HARS (*n* = 90) were available for most adult participants (age ≥ 18).

Demographic Analyses

There were group differences between diagnoses in sex, $\chi^2(3) = 8.71$, $p = .033$, driven by more male than female participants having no diagnoses but more females than males having any diagnosis, $\chi^2(1) = 7.8$, $p = .005$, and by a higher proportion of females being diagnosed with depression only than all other groups, $\chi^2(1) = 5.0$, $p = .025$. For family risk of depression, group differences, $\chi^2(3) = 13.13$, $p = .004$, were driven by the comorbid group disproportionately being descendants of a proband with depression compared to all other groups, $\chi^2(1) = 12.7$, $p < .001$. Differences for age, $F(3,108) = 7.35$, $p < .001$, and follow-up pairwise comparisons with Bonferroni correction revealed that the "none" group was younger than the depression only, $t(108) = -2.79$, $p = .038$, and comorbid groups, $t(108) = -4.22$, $p < .001$; in addition, the anxiety only group was younger than the comorbid group, $t(108) = -3.26$, $p = .009$. There were also group differences in HARS scores, $F(3, 86) = 2.90$, $p = .040$, but no group was significantly different compared to the other three. HDRS scores did not differ across groups, $F(3, 88) = 1.26$, *ns*. In terms of current depressive episodes[1], group differences, $\chi^2(3) = 8.31$, $p = .040$, were driven by the "none" group having no individual with a current episode, $\chi^2(3) = 4.20$, $p = .040$, and the comorbid group having 6 individuals with a current episode, $\chi^2(3) = 4.56$, $p = .033$. For current anxiety, a single subject in the comorbid group presented with generalized anxiety disorders, but there was no statistical difference across groups. The focus of this report is on *lifetime* depression and anxiety diagnoses before the EEG and dichotic tests. Relatively few individuals in each group had *current* depressive or anxiety diagnoses when these tests were given.

[1] One participant in the lifetime anxiety-only group presented with a current depressive episode. We repeated subsequent analyses with this individual classified under the comorbid group instead, revealing no changes to the results. For the purpose of the current report, this participant was assigned to the anxiety-only group.

Additionally, current use of psychotropic medication (i.e., sedatives, stimulants, antidepressants, anticonvulsants, and lithium, but excluding over the counter medications) within the last 3 months was observed for 20 participants (18%), revealing a group difference, $\chi^2(3) = 15.0$, $p = .002$ (Depression, $n = 3$; Anxiety, $n = 1$; Comorbid, $n = 13$; None, $n = 3$). This effect was driven by fewer participants in the anxiety only group using psychotropic medication than the other three groups combined, $\chi^2(1) = 5.2$, $p = .023$, and by more participants in the comorbid group using psychotropic medication than all other groups combined, $\chi^2(1) = 13.8$, $p < .001$. Similarly, current use of medication to treat physical problems (i.e., including cancer, cardiovascular disease, thyroid disorder, arthritis, autoimmune disorder, skin conditions, liver, kidney, allergies or respiratory disease, among others) was observed for 63 participants (56%) and also differed between groups, $\chi^2(3) = 9.59$, $p = .022$ (Depression, $n = 11$; Anxiety, $n = 16$; Comorbid, $n = 25$; None, $n = 11$). This effect was driven by fewer participants in the "none" group using physical medication than those in all other groups, $\chi^2(1) = 7.5$, $p < .001$, and by more comorbid participants using physical medication than all other groups, $\chi^2(1) = 5.9$, $p = .015$. Finally, current use of non-prescribed substances (i.e., alcohol and illicit substances, including cannabis, cocaine, heroin, etc.) was reported in 10 participants (9%) revealing no group difference, $\chi^2(3) = 2.66$, *ns* (Depression, $n = 3$; Anxiety, $n = 1$; Comorbid, $n = 4$; None, $n = 2$). The time point of last consumption of non-prescribed substances was at least 24 hours before data collection as determined via a standard baseline questionnaire administered to participants at the time of testing to screen for general compliance with testing instructions. Lifetime substance abuse was reported in 46 participants (41%) which also revealed no group difference, $\chi^2(3) = 4.14$, *ns* (Depression, $n = 10$; Anxiety, $n = 12$; Comorbid, $n = 16$; None, $n = 8$). Additional information for other current DSM diagnoses such as drug use disorder, alcohol use disorder,

attention deficit hyperactive disorder, and adjustment disorder affected less than 5 individuals having any of these diagnoses, and there was no difference between groups.

ERP measures from the Emotional Hemifield Task

Task, data acquisition, and processing procedures have been detailed in prior reports (e.g., Kayser et al., 1997, 2000, 2015a, 2016). Briefly, for the present dataset, 72-channel EEGs were acquired while pictures depicting facial areas of dermatological patients either before (negative) or after (neutral) surgical treatment were briefly presented for 250 ms to the left or right visual field. The stimulus set consisted of 16 highly-controlled pairs of pictures obtained from a textbook and plastic dermatological surgery that have been thoroughly evaluated with self-report ratings of pleasantness and arousal (e.g., Kayser et al., 2016) and skin conductance response (Kayser, 1995) in prior studies, revealing high construct validity of the intended manipulation of negative and neutral valence. Participants were instructed to focus on a fixation cross in the middle of the screen during presentation. During this passive-viewing paradigm, no response was required to intentionally minimize cognitive task demand, thereby exploiting the inherent affective value of the stimuli (for an extended rationale, see Kayser et al., 1997). Stimuli were presented in a pseudo-randomized sequence of 4 blocks with 32 trials per block. Artifacts (e.g., blinks, electrolyte bridges, drifts, movements, muscle activity, etc.) were identified and removed or reduced via an established pipeline of screening routines. Task engagement was monitored with horizontal eye movements, although robust enhancements of early ERP components contralateral to the exposed hemifield also attested to the paradigm validity (e.g., Kayser & Tenke, 2015a). Trials with horizontal eye movements exceeding 2º from baseline were rejected as it was taken to mean participants were not maintaining fixation, and corresponding trials

involving the same negative-neutral stimulus pair were also rejected (see Kayser et al., 2016, for further details on artifact removal and interpolation or rejection of artifactual trials). ERPs were computed from artifact-free trials for four conditions stemming from the combination of emotional content (negative, neutral) and hemifield (left, right), yielding means (±SD) of 28.92 ± 4.01 (range 14 to 32, Median = 30) trials per condition (due to the balanced rejection of artifact trials, all conditions have the same mean and standard deviation).

The ERP waveforms were transformed to reference-free current source density (CSD) estimates that represent radial current flow at scalp (e.g., Kayser & Tenke, 2015a, 2015b). CSD waveforms were submitted to temporal principal component analysis (tPCA) derived from the covariance matrix, followed by unrestricted Varimax rotation of covariance loadings (Kayser & Tenke, 2003). Of three consecutive CSD-tPCA components that revealed robust effects of emotional content, all of which were considered subcomponents of the LPP (Kayser et al., 2016, 2017), the present analysis focused on a prominent mid-parietal P3 source (385 ms peak latency), for which the emotional effects were attributed to differential activations of bilateral posterior cingulate cortex (Kayser et al., 2016). P3 source estimates were computed by pooling across six posterior-occipital sites (i.e., PO4, P6, P8, PO8, PO10, and O2 for right hemisphere and at homologous left hemisphere sites; Kayser et al., 2016). Figure 1 shows grand mean CSD waveforms for two representative right-hemispheric occipitoparietal sites (P8, PO8), revealing reduced emotional P3 effects (i.e., smaller difference between negative and neutral stimuli) for individuals with any diagnosis compared with those having no diagnosis.

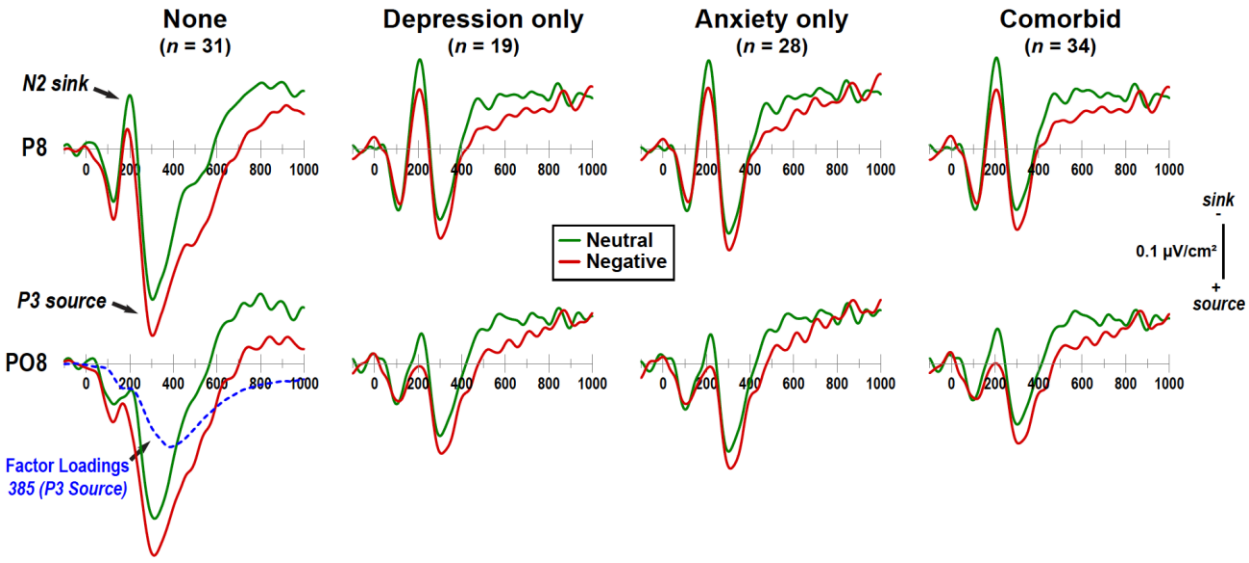

Figure 1. Current source density (CSD) [µV/cm²] waveforms (-100 to 1000 ms, 100 ms pre-stimulus baseline) for negative and neutral stimuli at selected right parietal-occipital sites (P8, PO8) for each diagnosis. Factor loadings optimally representing P3 source activity (peaking at 385 ms; see Kayser et al., 2016) are also shown at PO8 for individuals with no diagnosis.

Ear asymmetry measures from Dichotic Emotion Recognition Task

Task procedures have been detailed in Bruder et al. (2016). Briefly, participants listened to dichotically presented words pronounced in four different emotional tones (angry, happy, sad or neutral). On each trial, two words with different emotional intonations were simultaneously presented to each ear and participants were required to mark the perceived emotions (one from each ear) on an answer sheet, which consisted of line drawings of emotional faces representing the 4 possible emotions. Stimuli were presented at 73 dB SPL in each ear with a 5-s intertrial interval, during which participants had to mark their answers. Reaction time was not measured. Auditory accuracy scores were obtained for each ear and each emotion, computed as the percentage of correct responses over the total of 144 trials. For such tasks, the difference in

accuracy for right and left ear is typically used as a measure of perceptual asymmetry (e.g., Hugdahl, 2009). Following Bruder et al. (2016), we computed PA (left ear minus right ear accuracy) to target the left ear/right hemisphere advantage in the emotional recognition task.

The Emotional Hemifield Task and the Dichotic Emotion Recognition Task are not completely comparable due to differences in sensory modality and response requirement, but for as close a comparison as possible, the PA analyses focused only on sad and neutral word intonations. In this way, both visual and auditory tasks compared only stimuli of negative (unpleasant or sad) or neutral valence. Of the four emotions, anger and happiness are associated with approach motivation, while sadness, similar to disgust (likely the closest emotion associated with the dermatological 'before' pictures), is considered a withdrawal-oriented emotion (Harmon-Jones et al., 2009; Harmon-Jones, Harmon-Jones & Summerell, 2017). Furthermore, there was no significant difference between depression and no-depression groups for the happy or angry stimuli in the Dichotic Emotion Recognition Task (Bruder et al., 2016). In participants without depression, the right-hemispheric advantage for happy stimuli was also smaller than for sad stimuli (Bruder et al., 2016). Accordingly, we did not include happy or angry stimuli and only selected sad and neutral conditions in the auditory task to maximize emotional effects and minimize the discrepancies between the auditory and visual emotional paradigms.

Statistical Analysis

First, we evaluated whether the visual P3 and auditory accuracy measures are independently associated with lifetime history of internalizing disorders. For each measure, we performed separate 4 × (2 × 2) mixed ANOVA with diagnostic group (none, depression only, anxiety only, comorbid depression and anxiety) as a between-subjects variable, and hemisphere (left vs right) and emotion (negative or sad vs neutral) as within-subjects variables. A sensitivity analysis

(G*power; Faul et al., 2007) for a sample size of $N = 112$, $\alpha = 0.05$, 80% power (1-β), and an estimated correlation of $r = 0.66$ among repeated measures revealed the ability to detect small-to-medium effect sizes ($f = 0.13$; Cohen, 1988).

Second, we calculated a single value for P3 in the visual task and ear asymmetry in the dichotic listening task, entering both values as terms in a multinomial logistic regression in Stata (StataCorp, 2015), to examine the combination of both measures for predicting lifetime history of diagnosis (depression, anxiety or comorbid disorder versus none). The single visual P3 measure focused on difference in P3 source amplitude between negative and neutral stimuli over the right posterior-occipital region (termed $P3_{RH}$). This was calculated by subtracting the P3 factor score of the neutral condition from the negative condition. Auditory accuracy was transformed to perceptual asymmetry (PA), representing the difference between sad and neutral conditions in terms of left ear/right hemisphere advantage scores. In this way, based on our existing findings of hemispheric asymmetry, we were able to selectively target right-lateralized emotional processing with a single visual ERP ($P3_{RH}$) and auditory behavioral (PA) measure. Finally, $P3_{RH}$ and PA were converted into Z-scores (Z-score range: $P3_{RH}$ [-2.22 to 3.29]; PA [-2.90 to 2.77]) to normalize the metrics for each task that entered into the logistic regression analysis. A sensitivity analysis with a sample size of $N = 112$, $\alpha = 0.05$, 80% power (1-β), revealed the ability to detect odds ratios of 1.77 (or 0.56) for every standard deviation increase (or decrease) in predictor variables, a small effect size (Chen et al., 2010; Ferguson, 2009). Follow-up tests were conducted with simple effect coefficients to evaluate the basis for any significant interaction.

Results

Visual P3 in Emotional Hemifield Task

The split-plot ANOVA revealed significant main effects for all independent variables (Table 2, Visual P3). P3 amplitude was larger over the right than left hemisphere (*M* ± *SD*, 0.81 ± 1.05 vs 0.55 ± 0.85), and larger for negative than neutral stimuli (0.79 ± 0.95 vs 0.57 ± 0.81). A post-hoc Tukey test showed greater P3 amplitude in "none" group participants (1.15 ± 1.10) than in those with a lifetime diagnosis of depression (0.25 ± 0.54, $p = .001$) and comorbid diagnosis (0.38 ± 0.70, $p = .001$). There was marginally greater P3 amplitude in participants with a lifetime diagnosis of anxiety (0.82 ± 0.66) than those with depression ($p = .084$). Figure 2A shows the P3 amplitude for each diagnosis group, split by hemisphere and emotion condition.

Auditory Accuracy in Dichotic Listening Task

The respective split-plot ANOVA revealed significant main effects of hemisphere and emotion (Table 2, Auditory Accuracy). Auditory accuracy was higher for the left ear/right hemisphere than right ear/left hemisphere performance (86.8 ± 10.0 vs 83.8 ± 9.9), and higher for neutral than sad stimuli (90.5 ± 9.2 vs 80.2 ± 11.2). An interaction between hemisphere and emotion originated from greater left ear/right hemisphere accuracy for sad (left vs right ear, 82.9 ± 13.8 vs 77.3 ± 13.5, $t(108) = 4.01$, $p < .001$), but not for neutral stimuli (90.7 ± 10.4 vs 90.3 ± 9.3, $t(108) = 0.44$, *ns*). There was also a hemisphere by diagnosis interaction approaching significance. Analyses of simple effects revealed a right-greater-than-left hemispheric asymmetry for "none" group participants, 88.1 ± 6.0 vs 84.2 ± 8.1, $t(108) = 2.45$, $p = .016$, and those with an anxiety diagnosis, 87.8 ± 9.8 vs 81.5 ± 9.7, $t(108) = 3.71$, $p < .001$, but not for those with a depression, 84.2 ± 12.4 vs 83.9 ± 10.5, $t(108) = 0.18$, *ns*, or comorbid diagnosis, 86.2 ± 11.6 vs 85.2 ± 11.3, $t(108) = 0.66$, *ns*. There was no main effect of diagnosis, and follow-up tests for overall differences in accuracy between diagnoses were also not significant. Figure

2B shows auditory accuracy for each diagnosis group, split by hemisphere and emotion condition.

Table 2. Summary of split-plot ANOVAs for visual and auditory tasks (N = 112).

	df1	*df2*	*F*	*p*	η_p^2
Visual P3					
Hemisphere	1	108	12.16	.001	.101
Emotion	1	108	41.76	< .001	.279
Diagnosis	3	108	7.30	< .001	.169
Auditory Accuracy					
Hemisphere	1	108	11.19	.001	.094
Emotion	1	108	107.24	< .001	.498
Hemisphere × Emotion	1	108	11.16	.001	.094
Hemisphere × Diagnosis	3	108	2.47	.066 *	.064

Note. Only effects with $p \leq .10$ are listed. Effect sizes are listed as partial eta square (η_p^2).

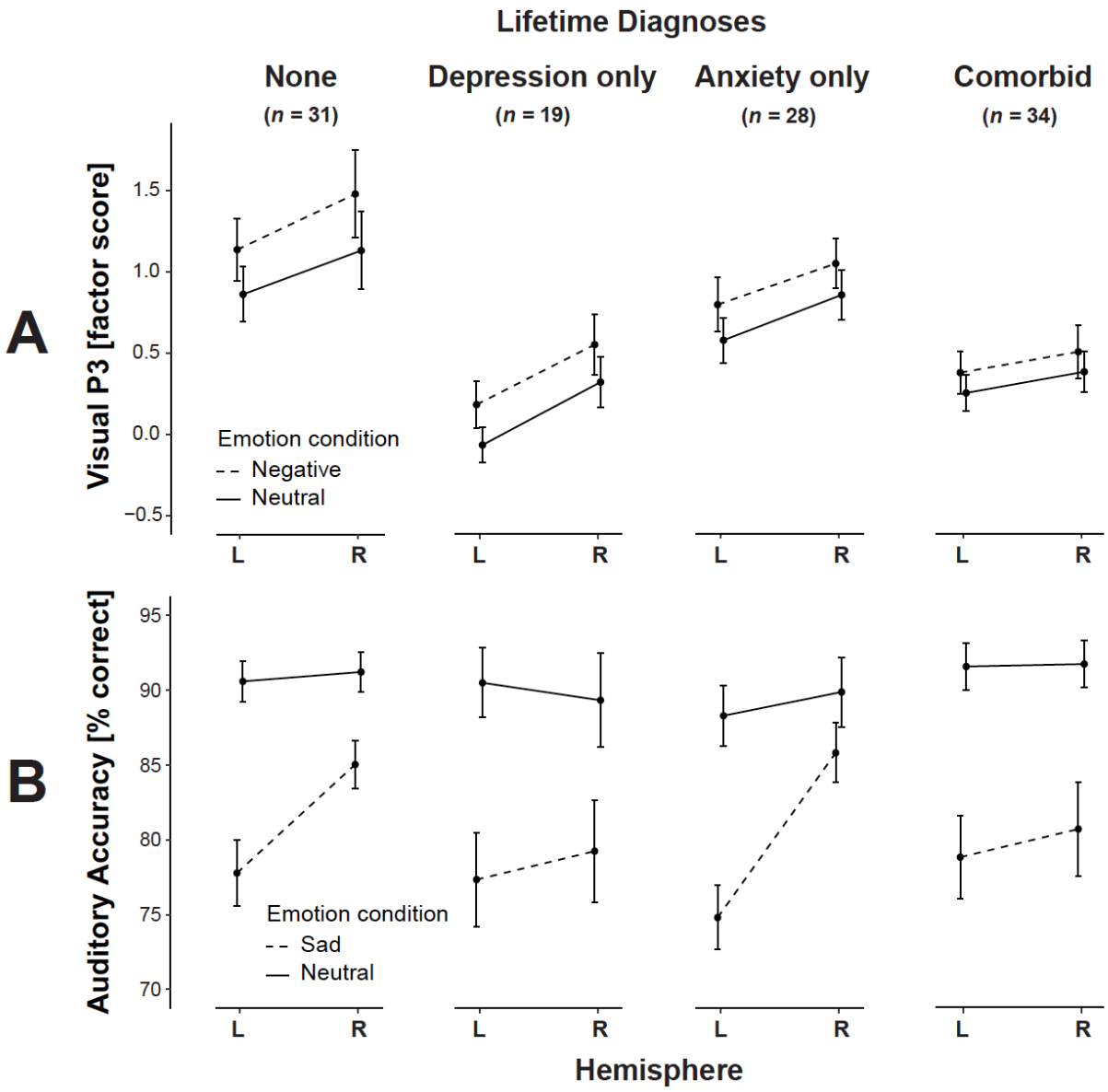

Figure 2. Mean (±SEM) visual P3 amplitude (A) and auditory accuracy (B) scores plotted separately for each diagnosis, emotion condition and hemisphere (L: Left, R: Right). Note that *right* hemisphere in auditory accuracy refers to *left* ear accuracy.

Given that approximately half of the "none" group was categorized as high risk for depression, we controlled for the possibility that familial risk influenced the P3 and PA measures, by comparing the measures of $P3_{RH}$ and PA between the high and low risk groups

across the whole sample. There was no significant difference between risk groups for $P3_{RH}$, $t(110) = 1.07$, *ns*; nor for PA, $t(110) = 1.64$, *ns*. We also compared these two measures between the high and low risk participants in the "none" group specifically, and there was no difference as well ($t(29) = 0.68$, *ns*, and $t(29) = 1.34$, *ns* for $P3_{RH}$ and PA respectively).

Predicting lifetime diagnoses with $P3_{RH}$ and PA measures

The above ANOVA results informed the calculation of a single measure to represent right hemisphere processing of negative emotional stimuli for the visual ERP ($P3_{RH}$) and dichotic (PA) tasks, as detailed under Methods. The omnibus model for the multinomial logistic regression was statistically significant, χ^2 (9) = 21.84, Nagelkerke $R^2 = .19$, $p = .009$. The interaction between visual $P3_{RH}$ and auditory PA measures predicted a lifetime depression diagnosis as opposed to no diagnosis ("none" group) but did not predict a lifetime anxiety or comorbid diagnosis. Main effects of $P3_{RH}$ and PA were present for predicting comorbidity of depression and anxiety, but not for either diagnosis alone (Table 3).

Table 3. Summary of multinomial logistic regression analysis ($N = 112$).

	b	*SE (b)*	*P*	*Odds Ratio* [95% *CI*]
Depression disorders				
$P3_{RH}$				
PA				
$P3_{RH}$ × PA	0.92	0.36	.011	2.50 [1.23, 5.08]
Anxiety disorders				
$P3_{RH}$				
PA				
$P3_{RH}$ × PA				
Comorbid disorders				
$P3_{RH}$	-0.78	0.32	.013	0.46 [0.25, 0.85]
PA	-0.64	0.31	.042	0.53 [0.29, 0.98]

$P3_{RH}$ × PA	

Note. *b*: Predictor coefficients for the regression model predicting a diagnosis of depression, anxiety, or comorbidity. The baseline or reference category is "None" (no diagnosis). Only significant effects ($p \leq .05$) are detailed. *CI* = confidence interval. $P3_{RH}$: difference in P3 source amplitude between negative and neutral stimuli over the right posterior-occipital region; *PA*: difference between sad and neutral conditions in terms of left ear/right hemisphere advantage scores.

For the depression only diagnosis, an increase in the interaction term was associated with an increased probability. Having both an increase in $P3_{RH}$ and PA or a decrease in both variables would result in a more positive interaction term and therefore greater probability of a diagnosis of depression alone (Figure 3). The smaller both $P3_{RH}$ and PA values are, that is, the smaller the electrophysiological and behavioral differences between negative and neutral conditions and therefore the weaker the discrimination between these emotional stimuli, the more likely an individual is to have a diagnosis of depression, as shown by the red (black) area in the bottom left of the heatmap in Fig. 3. However, having larger values of both $P3_{RH}$ and PA would also result in an increase in the interaction term and an increase in probability of a depression alone

diagnosis, shown by the red (black) area in the upper right of Fig. 3.

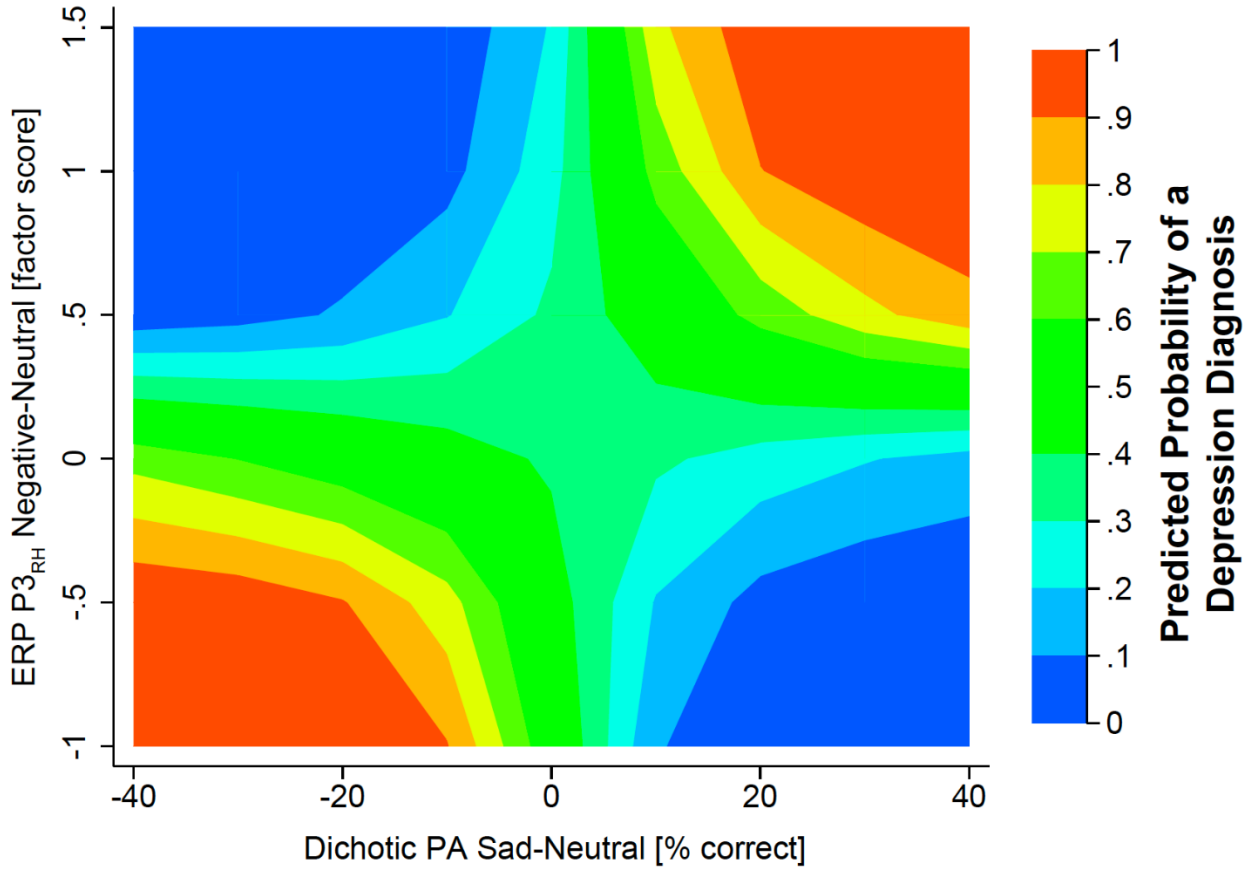

Figure 3. Representation of probability of a lifetime depression diagnosis at all levels of visual $P3_{RH}$ and auditory PA. The red (black) area equals high odds and the blue (light gray) area equals low odds of comorbid depression and anxiety. Although Z-scores were used for the regression analysis, the heat map is plotted in the original units of each variable for improved interpretability.

To probe this interaction, the Delta-method in Stata was used, with simple effect coefficients computed for three values of $P3_{RH}$, representing greater $P3_{RH}$ in the neutral than negative condition (Z-score = -2.5), no difference between neutral and negative conditions (Z-score = 0), and greater $P3_{RH}$ in the negative than neutral condition (Z-score = 3.5). The Z-scores reflect

approximate minimum and maximum scores. With a negative Z-scored $P3_{RH}$, an increase in the PA variable was associated with a decreased probability of a depression diagnosis (dydx = -.22, p = .009; see Fig. 2 where $P3_{RH}$ raw score is approximately -1). With $P3_{RH}$ at 0 (raw score approximately 0.3), an increase in the PA variable was associated with a nonsignificant change in the probability of a depression diagnosis. With the positive Z-scored $P3_{RH}$, an increase in the PA variable was associated with an increased probability of a depression diagnosis (dydx = -.31, p < .001; see Fig. 2 where $P3_{RH}$ raw score is approximately 1.5).

For comorbidity of depression and anxiety, an increase of each predictor was associated with a decrease in the probability of diagnosis. For ease of interpretability of the odds ratio (OR), we ran a separate logistic regression with comorbidity set as the baseline instead of no diagnosis, thus deriving ORs of 2.19 and 1.90 for $P3_{RH}$ and PA respectively, representing the increased odds of a comorbid diagnosis for a *decrease* of each predictor. The highest probability for a comorbid diagnosis is at low levels of *both* $P3_{RH}$ and PA, as shown by the red (black) area in the bottom left corner of the corresponding heat map (Figure 4). Conversely, the lowest probability of having a comorbid diagnosis is at high levels of both measures, as indicated by the blue (light gray) area in the top right corner of the heatmap.

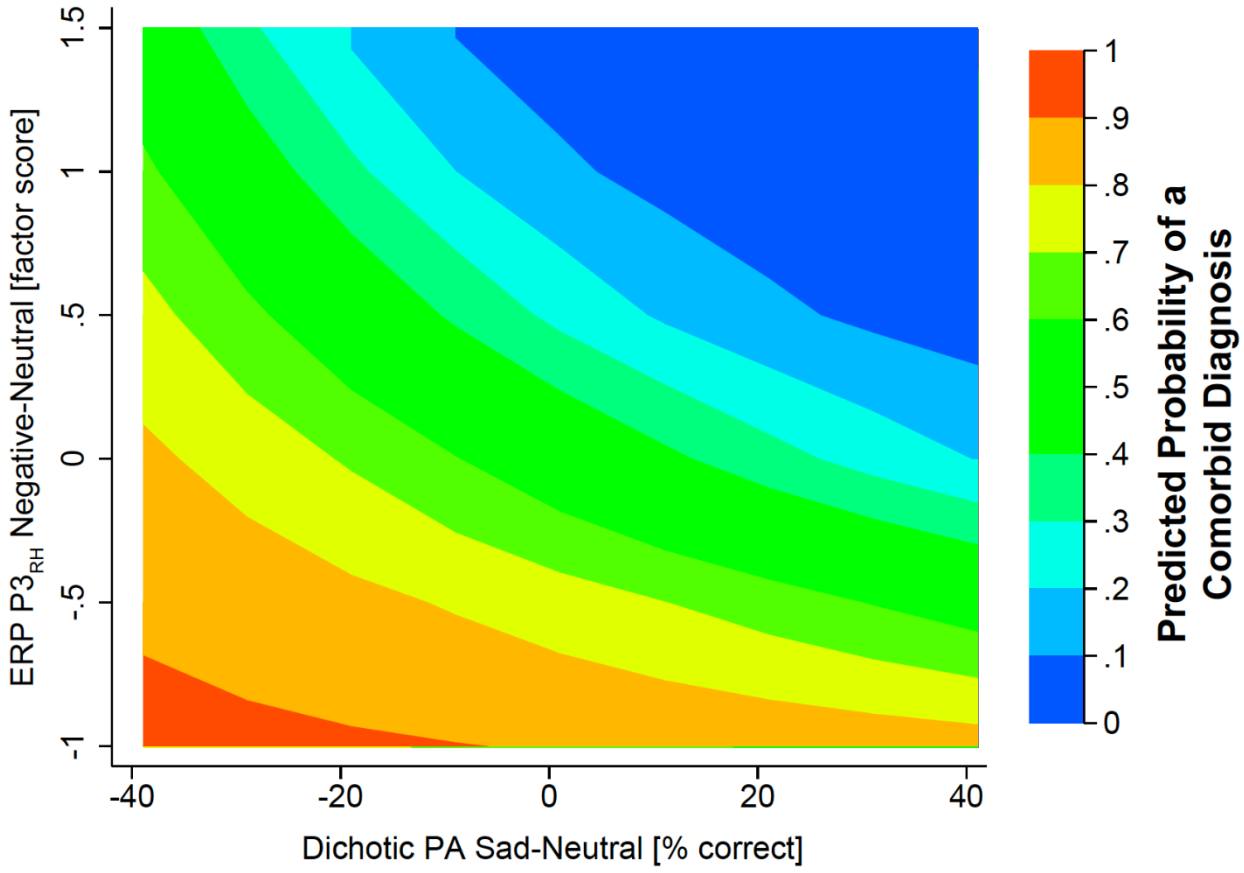

Figure 4. Representation of probability of a lifetime comorbidity diagnosis at all levels of visual $P3_{RH}$ and auditory PA (units as in Fig. 3).

Although we included adolescents in the current sample given that the P3 in response to emotional stimuli appeared to be stable throughout development (Pegg et al., 2019), there are well-known age-related changes in P3 for cognitive tasks (e.g., Bourisly, 2016; van Dinteren et al., 2014). To account for possible developmental changes during adolescent brain maturation, we repeated the ANOVAs and multinomial logistic regression for the adults-only subsample (n = 95; see Supplementary Material). Results were highly comparable to those stemming from the full sample, despite main effects of $P3_{RH}$ and PA being rendered to marginal significance (p <

.10) in predicting comorbidity of depression and anxiety, a likely consequence of reduced statistical power.

Exploratory analyses for current symptom severity

Given the partial overlap of findings for a depression and comorbid diagnosis, where both groups showed reduced visual $P3_{RH}$ and auditory PA, we also conducted additional exploratory analyses using HDRS[2] scores. Of the full sample, 94.7% and 88.2% of HDRS data were available for depression and comorbid groups respectively (missing data were for 3 participants or those under 18 who were not administered the adult rating scales). This available measure of depression severity could provide insights regarding the relation of *current* severity of depressive symptoms and remission on $P3_{RH}$ and PA so as to better interpret our findings. We computed the individual Z-score average of the $P3_{RH}$ and PA measures and correlated this combined metric with the available HDRS total score for the depression (n = 18, M_{age} = 38.2, SD = 13.6) and comorbid (n = 30, M_{age} = 41.8, SD = 9.4) diagnostic groups combined. Lower combined $P3_{RH}$ and PA scores were associated with higher depression scores, r = -.43, p = .003. We also used a double median split of $P3_{RH}$ and PA metrics to group these 48 individuals into 4 quadrants, and compared the group with low $P3_{RH}$ and PA (n = 18, M_{age} = 39.0, SD = 10.1) versus the group with high $P3_{RH}$ and PA (n = 10, M_{age} = 38.5, SD = 4.2). An independent samples t-test (equal variances not assumed) showed that the low $P3_{RH}$ and PA subgroup had higher HDRS scores than the high $P3_{RH}$ and PA subgroup, 5.56 ±6.93 vs 0.60 ±1.08, t(18.45) = 2.97, p = .008.

Discussion

Building on prior findings (Kayser et al., 2017; Bruder et al., 2016), this report aimed to explore if right-lateralized emotional processing across different visual and auditory tasks using

[2] Analogous analyses were run with the HARS, yielding nearly identical results, which is consistent with the fact that HDRS and HARS were highly correlated (r = .90).

electrophysiologic and behavioral measures could distinguish between clinical diagnoses of internalizing disorders. By firstly employing a more precise diagnostic categorization of disorders than used in Kayser et al. (2017) and Bruder et al. (2016), namely by also accounting for comorbidity of anxiety and depression, and secondly using the diagnostic categorization as a dependent variable in our regression model, we confirmed and extended prior findings of the role of the right hemisphere in abnormal processing of visual and auditory emotional stimuli in affective disorders. Importantly, we obtained new findings highlighting the differences in emotion processing across depression, anxiety, and comorbid depression/anxiety, and found evidence that emotion-related visual P3 and auditory PA measures were predictive of depression or comorbidity of depression and anxiety within our logistic regression model.

In comparing the ANOVA results of the present study with the results of our two prior studies, it is important to note that some of the previously-reported results appear to not replicate. For the P3, Kayser et al. (2017) reported a group by emotion interaction effect, where individuals with a lifetime diagnosis of depression had a smaller difference between negative and neutral stimuli than individuals with no depression, while this group by emotion interaction effect was absent in present analyses in largely the same sample. Similarly, for the PA, Bruder et al. (2016) reported a group by hemisphere interaction, where individuals with a lifetime diagnosis of depression had a smaller hemispheric asymmetry for sad stimuli than those without depression. This group by hemisphere interaction was only of borderline significance in the present analyses. These differences are likely due to the present analyses grouping participants into four groups, while the previous analyses used two groups (depression vs. no depression) which included the comorbid participants in the depression group. As seen in Fig. 2A, the “none” group showed a significant difference between the negative and neutral emotion conditions, but the depression

and comorbid groups did not. In Fig. 2B, the “none” group showed a significant right hemispheric advantage, but the depression and comorbid groups did not. This suggests that there is no difference in the direction of the effects, but only in the different grouping system used in the present report. Indeed, when we ran these analyses with a depression (depression only and comorbid groups) versus no depression (anxiety only and “none” groups) split, the P3 group by emotion interaction and the PA group by hemisphere interaction from Kayser et al. (2017) and Bruder et al. (2016) respectively were both replicated. Thus, including comorbidity as a separate category and thus separating out individuals with depression only or depression and anxiety improved the precision of diagnostic grouping, but unsurprisingly also modulates the group by emotion or hemisphere interactions observed for the full sample not grouped into additional diagnostic categories.

When processing negative emotions in the visual ($P3_{RH}$) and auditory (PA) domains, people with a lifetime diagnosis of “anxiety only” performed similarly to those with no diagnosis, which differs from the findings for those with a depression or comorbidity diagnosis. The logistic regression findings also showed that visual and auditory measures of emotion processing were not predictive of a lifetime anxiety diagnosis (as opposed to no diagnosis). Thus, we did not find evidence of a difference in emotion discrimination in anxiety compared to the no diagnosis groups. Although a previous study found increased LPP to unpleasant versus neutral pictures in individuals having GAD (MacNamara et al., 2016), there were some notable methodological differences in the experimental tasks and ERP data processing, which impedes a direct comparison of their findings regarding emotion processing in anxiety to those in present study. For example, MacNamara et al. (2016) used neutral and unpleasant IAPS images as stimuli with foveal presentations, whereas the present report relied on the emotional hemifield task that

employed matched pairs of diseased and healthy (after treatment) dermatological face stimuli with lateralized presentations. Furthermore, MacNamara et al. (2016) analyzed surface potentials referenced offline to the average of two mastoids, with LPP pooled across midcentroparietal scalp sites (CP1, CP2, Cz and Pz), whereas Kayser et al. (2017) used a data-driven, reference-free CSD-tPCA approach to identify and distinguish LPP subcomponents over the right occipitoparietal sites in a more fine-grained fashion. That said, the present findings revealed that emotion processing operationalized by $P3_{RH}$ and PA metrics was similar in individuals with an anxiety only lifetime diagnosis and "none" group individuals.

The deficits in $P3_{RH}$ and PA seen for both the depression only and comorbid groups support hypotheses of impaired emotional processing in individuals having a depressive disorder. Our results are consistent with the emotional context insensitivity (ECI) theory, which posits that depression is associated with a blunted reactivity towards unpleasant stimuli (e.g. Rottenberg, Gross & Gotlib, 2005; Proudfit et al., 2015). With regard to comorbidity, MacNamara et al. (2016) suggested that affective blunting in depression still persists when controlling for the presence of GAD. Similarly, we found a higher probability for a lifetime diagnosis of depression and depression comorbid with anxiety when individuals had low right hemisphere processing of negative stimuli across tasks (lower left quadrants in Figs. 3 and 4). However, we did find evidence of differences in the prediction of depression as opposed to comorbidity in individuals with high levels of emotion discrimination and reactivity (upper right quadrants in Figs. 3 and 4). High levels of both $P3_{RH}$ and PA were predictive of increased probability of lifetime diagnosis of depression alone, but not comorbidity, indicating that comorbidity alters the relationship between depression and right-hemispheric emotional processing to some extent.

Notably, the findings of the interaction effect of $P3_{RH}$ and PA on the depression only group was preserved after removing participants younger than 18, and also after the inclusion of selected covariates - demographic and clinical variables that were not equally distributed across diagnostic groups (see Supplementary Material for these analyses). However, restricting the sample to adults altered the effects on a comorbid diagnosis by lessening the predictive main effects of $P3_{RH}$ and PA, and the inclusion of age as a covariate removed the predictive effect of $P3_{RH}$ but not PA for comorbity. Furthermore, the age confound might explain the absence of results for the anxiety only group, as the anxiety only and "none" groups were younger and of similar age ranges than the depression only and comorbid groups. While it is premature to overinterpret the inherent limitations stemming from uncontrolled differences in age between these post-hoc diagnostic categorizations, emotional processing may change with age. Still, the supplementary age-related analyses did not alter the interaction effect of predicting depression; instead, this predictive finding was strengthened. Considering there were no age differences between the comorbid and depressed groups, we conclude that the interaction of $P3_{RH}$ and PA is specific for predicting depression alone and is unlikely due to group differences in age or other potential demographic confounds.

We also examined the relationship between current depression symptom severity and a combined metric of $P3_{RH}$ and PA. Although lower $P3_{RH}$ and PA was most evident in individuals with greater HDRS depression ratings, interestingly, both low and high levels of $P3_{RH}$ and PA were predictive of increased probability of lifetime diagnosis of depression. Low levels of $P3_{RH}$ and PA are indicative of reduced differentiation and reactivity to negative as opposed to neutral emotional stimuli, whereas high levels of $P3_{RH}$ and PA could reflect *enhanced* reactivity to negative emotional stimuli. It is tempting to speculate that low right hemispheric processing or

reactivity to negative emotional stimuli may be predictive of a specific form of depression that differs from that for high levels, such as melancholic versus atypical subtypes that differ in their emotional reactivity. According to the DSM-V, melancholic depression is defined by anhedonia, a loss of reactivity to emotional stimuli, and endogenous symptoms, such as loss of appetite and insomnia, whereas atypical depression exhibits some opposite symptoms, such as increased eating, hypersomnia, and rejection sensitivity. In this regard, prior studies have found that reduced right hemisphere advantage for dichotic or visual laterality tasks was most evident in depressed patients having a typical or melancholic form of depression (Bruder et al., 2017).

An alternative possibility is that, among individuals with lifetime depression, lower ratings of *current* depressive symptoms in those with high $P3_{RH}$ and PA were responsible for their more normal measures of right hemispheric emotional processing However, it should be noted that the HDRS has an emphasis on melancholic and physical symptoms of depression and does not assess atypical symptoms (Williams, 1988); thus, any atypical symptoms exhibited by individuals in the high $P3_{RH}$ and PA groups would not have been recorded. Due to the smaller sample size, our post-hoc exploration of the symptom data remains inconclusive. More clinical symptom data using the HDRS and the Atypical Depression Supplement (Williams & Terman, 2003) would be needed in a larger sample, together with visual ERP and auditory PA data, to replicate and validate our findings and establish their relationship to symptom severity or subtypes of depression.

Our findings of differences in right hemispheric emotion processing between and within internalizing disorders may have clinical implications for the improved diagnostics of depression and anxiety disorders, as well as for personalizing selection of specific antidepressant treatment or psychotherapy. Patients who have reduced right hemispheric activation to emotional stimuli

may benefit from a different treatment than patients who do not show this right hemispheric deficit, although this will require further research. This information could inform emotion-based intervention approaches to address unique features of the patient's condition. For example, "graded engagement" interventions involve behavioral activation and exposure techniques to target depression and anxiety, respectively, and can also be flexibly adjusted for comorbid disorders (Weersing et al., 2008). This approach is also able to target threshold and subthreshold levels of comorbidity (Weersing et al., 2008), which allows these interventions to effectively reduce functional impairment across the range of internalizing disorders. Furthermore, magnetoencephalography (MEG) studies revealed that parietal hypoactivation, associated with impaired emotional processing, normalized following successful electroconvulsive (Zwanger et al., 2016) or monopharmacotherapy (Domschke et al., 2015), suggesting a modifiable link between depression and impaired emotional responsivity. A recent study using transcranial direct current anodal stimulation to the right temporoparietal area also showed improvements on the verbal fluency of emotional words (Wilson et al., 2018). Although Wilson et al. (2018) found improvements in adults with autism, not depression, the results showed that an increased activation of right hemispheric regions led to increased emotional processing, which might in turn lead to decreased symptoms. Our findings support the further study of behavioral and electrophysiological measures that could assist in the development or selection of specific treatments that uniquely target emotional processing deficits in depression, anxiety, comorbid disorders, as well as subtypes of depression.

The current study has several limitations. First, the visual and auditory measures of emotion processing were employed in the analysis because these measures were readily available, as they had already been collected in a prior wave of the ongoing longitudinal study of families at risk

for depression (Weissman et al., 2016). Furthermore, the focus of this study was predicting *lifetime* depression and/or anxiety and not *current* disorders; participants in the "none" group, if examined a few years later, might develop a depression and/or anxiety disorder and would no longer be categorized as being in the "none" group. Thus, data collection was not designed per se to answer the research question posed here, which likely contributed to uneven diagnostic cell sizes and also limited the availability of clinical measures more suitable to distinguish anxiety from depression. While the post-hoc and exploratory nature of the analyses that capitalize on previously published data from Kayser et al. (2017) and Bruder et al. (2016) constitutes a limitation, it nevertheless sets the stage for future studies. Second, the two emotional responsivity measures are confounded with regard to stimulus (visual vs. auditory) and measurement (electrophysiology vs. behavior) domains, meaning these domains were not independently varied. However, while this limitation does not allow conclusions about the unique impact of either aspect, it also does not diminish the utility of either task measure as a valid index of emotional processing. Thus, future studies ought to consider other experimental paradigms and measures of emotion processing as well, to allow for a broader collection and representation of electrophysiological *and* behavioral data across sensory modalities. Additionally, the concept of emotion processing can be expanded to include emotion regulation as well, for more applicability to treatment-related research in emotional dysregulation. For instance, enhancing emotion regulation skills has been shown to improve efficacy of cognitive behavior therapy (CBT) for depression (Berking et al., 2013), and up- and down-regulation of emotional processes can be examined through activity in right temporoparietal and prefrontal regions (Davidson, Jackson & Kalin, 2000; Etkin, Buchel & Gross, 2015) to determine if emotional regulation can predict clinical health outcomes. Third, analyses were limited to the

umbrella diagnoses of depression and anxiety, without specifying diagnostic subtypes of these disorders. In fact, the current findings suggest that symptom and subtype considerations may be of critical relevance. In particular, given evidence of emotional processing and laterality differences between melancholic and atypical depression (Bruder et al., 2017), future studies should include further specification of clinical diagnosis and current symptoms. Finally, we note that a cross-sectional analysis fails to differentiate cause and effect between impaired emotion processing and diagnosis. Individuals with depression may have visual and auditory emotion processing impairments, or individuals with these impairments may be more vulnerable to developing depression. More hypothesis-driven studies, such as examining changes in emotion processing before and after treatment interventions, have to be conducted to better understand the direction of this relationship.

To conclude, the present findings suggest a relationship between two multimodal predictors targeting right hemispheric emotional processing – visual ERPs and auditory perceptual asymmetries –and lifetime diagnoses of internalizing disorders. Individuals who had reduced perceptual asymmetry for discriminating between sad and neutral word intonations, and had reduced right hemisphere ERP reactivity to negative than neutral pictures, were more likely to have a lifetime diagnosis of depression alone or comorbid with anxiety. An interaction between $P3_{RH}$ and PA measures predicted lifetime depressive disorder; however, comorbidity was separately predicted by $P3_{RH}$ and PA alone, noting that the $P3_{RH}$ effect was possibly confounded by group differences in age. Increased probability of a depression diagnosis was evident not only at lower levels of both predictors (i.e., lack of right hemispheric emotional reactivity or differentiation across modalities), but interestingly also at high levels of both predictors (i.e., heightened reactivity to negative emotional stimuli across modalities). Findings suggest that

reduced or heightened right-lateralized emotional reactivity to negative stimuli, when occurring across processing domains, is uniquely associated with depression. However, comorbidity appears to be linked to deficits of emotional processing in either domain. Of note, $P3_{RH}$ and PA were not predictive of lifetime diagnosis of anxiety disorder alone, suggesting that any potential deficits in emotion processing in individuals with anxiety is less discernable when compared with individuals with depression and comorbidity of both. These findings highlight the need for further study using measures of right hemisphere function related to emotion processing as markers for predicting development of depressive or comorbid disorders, and potentially for targeting of treatments for these disorders.

Author Note.

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Supplementary Material:

Dissociating Disorders of Depression, Anxiety, and their Comorbidity with Measures of Emotional Processing: A Joint Analysis of Visual Brain Potentials and Auditory Perceptual Asymmetries

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Supplement A: Demographics Analyses

Participants included in these supplemental analyses were aged 18 and older (n = 95). Table S1 below lists the demographics of this adults-only sample.

Table S1. Crosstabulation of diagnosis with sex and familial risk for depression, and corresponding means (±SD) of age.

Diagnosis	*N*	Sex		Family Risk[a]		Age
		M	F	High	Low	[min, max]
Depression only	18	6	12	9	9	38.2 ± 13.6 [18, 59]
Anxiety only	25	8	17	11	14	30.9 ± 10.9 [18, 49]
Comorbidity	31	13	18	26	5	42.3 ± 9.7 [21, 59]
None	21	13	8	8	13	31.9 ± 14.4 [19, 56]
Total	95	40	55	56	39	33.1 ± 13.9

Note. [a]Family Risk refers to whether the individual was a descendant of a proband originally diagnosed with depression or of a healthy control participant (Generation 1). All clinical variables are identical to those listed in Table 1 because these instruments were only administered to adults.

Demographic Analyses

There were no group differences between diagnoses in sex. For family risk of depression, group differences, $\chi^2(3) = 14.26$, $p = .003$, were driven by the comorbid group disproportionately being descendants of a proband with depression compared to all other groups, $\chi^2(1) = 13.7$, $p < .001$. Despite removing adolescents from the sample, there were still differences for age, $F(3, 91) = 5.45$, $p = .002$. Follow-up pairwise comparisons with Bonferroni correction revealed that the "none" group was younger than the comorbid group, $t(91) = -3.10$, $p = .016$; in addition, the

anxiety only group was younger than the comorbid group, $t(91) = -3.56$, $p = .004$. However, there was no longer a significant difference in age between the "none" group and the depression only group.

Additionally, current use of psychotropic medication (i.e., sedatives, stimulants, antidepressants, anticonvulsants, and lithium, but excluding over the counter medications) within the last 3 months was observed for 16 participants (17%), revealing an overall group difference, $\chi^2(3) = 17.8$, $p < .001$ (Depression, $n = 3$; Anxiety, $n = 0$; Comorbid, $n = 12$; None, $n = 1$). This effect was driven by fewer participants in the anxiety only group using psychotropic medication than the other three groups combined, $\chi^2(1) = 5.5$, $p = .019$, and by more participants in the comorbid group using psychotropic medication than all other groups combined, $\chi^2(1) = 11.3$, $p = .001$. Similarly, current use of medication to treat physical problems (i.e., including cancer, cardiovascular disease, thyroid disorder, arthritis, autoimmune disorder, skin conditions, liver, kidney, allergies or respiratory disease, among others) was observed for 62 participants (65%) but did not differ between groups, $\chi^2(3) = 5.22$, *ns* (Depression, $n = 11$; Anxiety, $n = 15$; Comorbid, $n = 25$; None, $n = 11$). Finally, use of non-prescribed substances (i.e., alcohol and illicit substances, including cannabis, cocaine, heroin, etc.) was reported in 6 participants (9%) revealing no group difference, $\chi^2(3) = 5.03$, *ns* (Depression, $n = 3$; Anxiety, $n = 0$; Comorbid, $n = 2$; None, $n = 1$). Lifetime substance abuse was reported in 42 participants (44%) but also revealed no group difference, $\chi^2(3) = 1.26$, *ns* (Depression, $n = 10$; Anxiety, $n = 10$; Comorbid, $n = 14$; None, $n = 8$).

Supplement B: ANOVA analyses for participants aged 18 and older (*n* = 95).

Visual P3 in Emotional Hemifield Task

The split-plot ANOVA revealed significant main effects for all independent variables (Table S2, Visual P3). P3 amplitude was larger over the right than left hemisphere (*M* ± *SD,* 0.55 ± 0.77 vs 0.38 ± 0.72), and larger for negative than neutral stimuli (0.55 ± 0.73 vs 0.38 ± 0.63), which is consistent with our prior findings (Kayser et al., 2016, 2017). A post-hoc Tukey test showed marginally greater P3 amplitude in healthy ("none" group) participants (0.64 ± 0.74) than in those with a lifetime diagnosis of depression (0.17 ± 0.44, $p = .096$), which is also in agreement with our prior reports. There was greater P3 amplitude in participants with a lifetime diagnosis of anxiety (0.79 ± 0.69) than those with depression ($p = .009$) and the comorbid group (0.25 ± 0.55, $p = .009$). Compared to the full sample, the adults-only subsample revealed the same main effects, with a few minor differences in the post-hoc Tukey test of P3 amplitude across diagnostic groups – greater P3 in healthy participants than comorbidity was no longer significant, and greater P3 in anxious participants than comorbidity was now significant.

Auditory Accuracy in Dichotic Listening Task

The respective split-plot ANOVA revealed significant main effects of hemisphere and emotion (Table S2, Auditory Accuracy). Auditory accuracy was higher for the left ear/right hemisphere than right ear/left hemisphere performance (86.9 ± 10.3 vs 83.3 ± 10.1), and higher for neutral than sad stimuli (90.5 ± 9.4 vs 79.6 ± 11.5), which is also consistent with our prior findings (Bruder et al., 2016). An interaction between hemisphere and emotion originated from greater left ear/right hemisphere accuracy for sad (left vs right ear, 82.9 ± 14.5 vs 76.3 ± 13.7, $t(91) = 4.03$, $p < .001$), but not for neutral stimuli (90.7 ± 10.7 vs 90.3 ± 9.4, $t(91) = 0.65$, *ns*).

There was also a hemisphere by diagnosis interaction, revealing a right-greater-than-left hemispheric asymmetry for healthy participants, 88.0 ± 6.0 vs 81.5 ± 7.7, $t(91) = 3.19$, $p = .002$, and those with an anxiety diagnosis, 89.0 ± 9.5 vs 82.5 ± 9.8, $t(91) = 3.53$, $p = .001$, but not for those with a depression, 84.9 ± 12.5 vs 84.1 ± 10.7, $t(91) = 0.36$, *ns*, or comorbid diagnosis, 86.9 ± 11.9 vs 84.6 ± 11.5, $t(91) = 0.54$, *ns*. There was no main effect of diagnosis, and follow-up tests for overall differences in accuracy between diagnoses were also not significant. Compared to the full sample, there were no differences in effects except for Hemisphere × Diagnosis for Auditory Accuracy being statistically significant instead of marginally significant. There were also no non-significant effects that became significant after the exclusion of participants younger than 18.

Table S2. Summary of split-plot ANOVAs for visual and auditory tasks ($n = 95$).

	df1	*df2*	*F*	*p*	η_p^2
Visual P3					
Hemisphere	1	91	6.22	.014	.064
Emotion	1	91	26.53	< .001	.226
Diagnosis	3	91	5.41	.002	.151
Auditory Accuracy					
Hemisphere	1	91	14.30	< .001	.136
Emotion	1	91	97.61	< .001	.518
Hemisphere × Emotion	1	91	13.03	.001	.125
Hemisphere × Diagnosis	3	91	2.94	.037	.088

Note. Only effects with $p \leq .10$ are listed. Effect sizes are listed as partial eta square (η_p^2).

Supplement C: Logistic regression for participants aged 18 and older (*n* = 95).

The omnibus model for the multinomial logistic regression was statistically significant, χ^2 (9) = 17.19, Nagelkerke R^2 = .18, *p* = .046. The interaction between visual $P3_{RH}$ and auditory PA measures predicted a lifetime depression diagnosis as opposed to no diagnosis (healthy) but did not predict a lifetime anxiety or comorbid diagnosis. Compared to analyses on the full sample, main effects of $P3_{RH}$ and PA were no longer statistically significant in predicting comorbidity of depression and anxiety, but effects were in the same direction at a trend level (Table S3). To check if this difference was due to a decrease in power or a change in means, we ran independent sample t-tests on the full comorbid group (*n* = 34) versus the adults-only comorbid group (*n* = 31) for $P3_{RH}$ and PA. There was no difference between these two groups for the two variables (P3RH: *t*(63) = 0.64, *ns*; PA: *t*(63) = 0.28, *ns*), thus this loss of statistical significance for the main effects in predicting comorbidity was likely due to the decreased sample size.

There were no other significant effects.

Table S3. Summary of multinomial logistic regression analysis (*n* = 95).

	b	*SE (b)*	*P*	*Odds Ratio* [95% *CI*]
Depression disorders				
$P3_{RH}$				
PA				
$P3_{RH}$ × PA	0.99	0.40	.013	2.67 [1.23, 5.88]
Anxiety disorders				
$P3_{RH}$				
PA				
$P3_{RH}$ × PA				
Comorbid disorders				
$P3_{RH}$	-0.65	0.35	.066	0.52 [0.26, 1.04]
PA	-0.58	0.34	.086	0.56 [0.29, 1.09]
$P3_{RH}$ × PA				

Note. *b*: Predictor coefficients for the regression model predicting a diagnosis of depression, anxiety, or comorbidity. The baseline or reference category is “None” (no diagnosis). Only

marginally significant effects ($p \leq .10$) are detailed. *CI* = confidence interval. $P3_{RH}$: difference in P3 source amplitude between negative and neutral stimuli over the right posterior-occipital region; *PA*: difference between sad and neutral conditions in terms of left ear/right hemisphere advantage scores.

Supplement D: Covariate analyses

Analyses here are based on the full sample ($N = 112$). Sex, family risk, age, and use of psychotropic and physical ailment medication were each added individually as a fixed effect to the regression model as these measures showed significant diagnoses group differences. Table S4 reports the interaction effect for predicting depression and two main effects for predicting comorbidity for each of the 5 additional models including a covariate. Except for age, the inclusion of a covariate did not alter any of the findings.

Table S4. Selected effects from follow-up multinomial logistic regression models with added covariates, one at a time.

Covariate	Diagnosis	Effect	*P*	*Odds Ratio* [95% *CI*]
Age	Depression only[a]	$P3_{RH} \times PA$	.008	2.44 [1.23, 4.73]
	Comorbid[b]	**$P3_{RH}$**	**.238**	**0.67 [0.35, 1.30]**
	Comorbid	PA	.009	0.39 [0.19, 0.79]
Family Risk	Depression only	$P3_{RH} \times PA$	.011	2.55 [1.24, 5.27]
	Comorbid	$P3_{RH}$	.024	0.48 [0.25, 0.91]
	Comorbid	PA	.087	0.57 [0.30, 1.08]
Sex	Depression only	$P3_{RH} \times PA$	.011	2.75 [1.26, 6.03]
	Comorbid	$P3_{RH}$	.018	0.47 [0.25, 0.88]
	Comorbid	PA	.044	0.53 [0.28, 0.98]
Psychotropic Medication	Depression only	$P3_{RH} \times PA$	.010	2.63 [1.27, 5.48]
	Comorbid	$P3_{RH}$	.017	0.46 [0.25, 0.88]
	Comorbid	PA	.080	0.57 [0.30, 1.07]
Physical Medication	Depression only	$P3_{RH} \times PA$	.012	2.46 [1.22, 4.97]
	Comorbid	$P3_{RH}$	.025	0.48 [0.25, 0.91]
	Comorbid	PA	.030	0.49 [0.25, 0.93]

Note. [a]Effect predicting the odds of a *depression* diagnosis. [b]Effects predicting the odds of a *comorbid* diagnosis. Effects are **bolded** when the corresponding finding without covariates was altered (cf. Table 3). Only marginally significant effects ($p \leq .10$) are detailed.

When age was added as a covariate, the interaction of $P3_{RH}$ by PA remained as a significant predictor of a diagnosis of depression and so did PA as a predictor of a comorbid diagnosis; however, $P3_{RH}$ was no longer a significant predictor of a comorbid diagnosis.