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Toward a neurobehavioral trait conceptualization of depression proneness

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Abstract

The etiology of major depressive disorder is heterogeneous, and differing pathways leading to the development of depression are proposed to account for alternative variants of depressive illness and their distinct comorbidity patterns. The present study was undertaken as a step toward developing a model for conceptualizing and quantifying dispositional proneness to depression, marked by reduced neural sensitivity to rewarding events and more persistent occurrence of depressive symptomatology. Using data for college and community adult participants ($N = 201$), we sought to quantify variations in depression proneness by combining symptom indicators of persistent depressive conditions (dysthymic disorder, depressive personality) with a brain potential response that has been shown to index sensitivity to pleasurable events—the reward positivity (RewP; Proudfit, 2015). We first extended prior work on the RewP and depression by showing that the magnitude of RewP covaried negatively with symptoms of persistent depressive conditions (dysthymia, depressive personality) but not with current levels of depression. Persistent depressive symptoms and the RewP were then combined to form a composite neuroclinical index of depression proneness. Compared to persistent depressive symptoms alone, this composite dimensional index showed improved specificity of relations with diagnostic criterion measures, that is, similar-level associations with other indicators of depression proneness but significantly lower associations with fear disorder symptomatology. These findings provide evidence that a dimension of depression proneness can be quantified effectively by combining psychological indicators of persistent depression with a neurophysiological index of a core depression-related process (i.e., reward sensitivity).

KEYWORDS

biomarker, depression, dysthymia, neuroclinical assessment, reward positivity, reward sensitivity

1 | INTRODUCTION

According to the National Comorbidity Survey, depressive disorders are among the most prevalent psychological problems, affecting more than 5% of all people annually and more than 16% throughout their lifetime (Kessler et al., 2003). However, cases of major depressive disorder (MDD) are complex in that they vary in terms of severity and clinical course and are often comorbid with other psychological disorders—in particular, anxiety-related

conditions (Mineka, Watson, & Clark, 1998). Furthermore, MDD occurs at elevated rates across groups of individuals showing distinct patterns of comorbidity (Vaidyanathan, Patrick, & Iacono, 2011), pointing toward equifinality in etiologic pathways to major depression (cf. Cicchetti & Rogosch, 1996) and a need to recognize variants of depressive pathology (Klein & Kotov, 2016). The current work was undertaken to evaluate whether use of a neurophysiological indicator of sensitivity to rewarding outcomes, the reward positivity (RewP; Proudfit, 2015), might enhance our ability to index a distinct variant of depressive illness marked by persistent and severe dysphoric symptomatology and reduced capacity for pleasurable engagement.

1.1 | Evidence for different pathways to depression

Factor analytic studies of anxious-depressive (internalizing) psychopathology (e.g., Kendler, Prescott, Myers, & Neale, 2003; Krueger, 1999) have shown that major depression contains a substantial portion of variance in common with other disorders in this spectrum, due to a shared component of negative affectivity (Clark & Watson, 1991; Krueger, McGue, & Iacono, 2001) reflecting generalized psychological distress and demoralization (Mineka et al., 1998; Tellegen et al., 2003). This overlapping component of variance poses challenges to achieving specificity in diagnostic assessments of depression. Some individuals may display depression secondarily to high levels of anxiety or fear that become unmanageable (Mineka et al., 1998). Other individuals may inherit a distinct disposition involving low sensitivity to reward that gives rise to anhedonic features at a young age and increases risk for development of MDD in adolescence (e.g., Nelson, Perlman, Klein, Kotov, & Hajcak, 2016). Individuals with this early emerging and more chronic form of depression are particularly likely to experience repeated episodes with high symptom severity (Klein & Hajcak, 2015). Despite similarities in clinical presentation, depression arising from different causal sources may call for separate treatment interventions and differ in clinical prognosis. For example, early age of onset and recurrent episodes (factors known to be associated with chronic and severe depressive illness) are strong predictors of MDD involving suicide attempts in adulthood (Harrington et al., 1994). Additionally, recent research by Klein and Kotov (2016) using a 10-year prospective longitudinal design to examine the chronicity and severity of depressive symptoms in an outpatient sample provides support for the idea of a qualitatively distinct subgroup of chronically depressed individuals. Findings from this project showed this variant of depression to be characterized by recurrent depressive episodes, more severe depressive symptoms, and more comorbid personality disorders when compared to other patients meeting MDD criteria at the onset of the study.

While MDD clearly has multiple distal and proximal factors that influence its onset, a substantial body of evidence indicates that certain individuals are specifically predisposed to develop depressive conditions. For example, one longstanding view (e.g., Gillespie, 1929; Monroe, Thase, Hersen, Himmelhoch, & Bellack, 1985) has been that a distinct liability for a particular variant of depressive illness, heritable in nature and transmitted from parents to children, heightens the propensity to exhibit depressive episodes across time. Consistent with this view, Vaidyanathan et al. (2011) identified a specific diagnostic subgroup within the National Comorbidity Survey (Kessler et al., 2003) that exhibited high rates of dysphoric disorders specifically—differentiated from other groups in particular by a high prevalence of dysthymia. In turn, dysthymia (termed persistent depressive disorder in the latest, 5th edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-5; American Psychiatric Association, 2013) has been theorized to reflect the presence of a distinct trait liability factor (Howland & Thase, 1991; Riso, Miyatake, & Thase, 2002) that is associated with earlier emerging, more recurrent MDD (Goodman & Barnhill, 1995; Griffiths, Ravindran, Merali, & Anisman, 2000). Relatedly, work by Klein (2010) has documented the existence of a chronic subtype of depression characterized by a greater presence of risk factors, and more marked impairment, than nonchronic depression. The idea of a specific dispositional liability for depression was also the basis for the provisional diagnosis of depressive personality disorder included in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000). However, to advance understanding of depressive illness that arises early in life and persists in a more severe manner across time, new assessment approaches are needed that incorporate indicators of depression-specific liability factors (Mendels & Cochrane, 1968).

1.2 | Using neurophysiology to refine depression phenotypes

Prominent theories have emphasized deficits in the capacity for positive affect or pleasure as a core element of depression (e.g., Clark & Watson, 1991; Lewinsohn & Libet, 1972), and dysfunction in neural systems for reward has been postulated as a mechanism for more persistent and severe depression. For example, Vrieze et al. (2013) reported that patients with MDD exhibiting distinct anhedonic features performed more poorly in a probabilistic reward-response task compared to healthy controls and nonanhedonic MDD patients, indicating a lack of sensitivity to rewarding outcomes in this MDD subgroup. A viable candidate indicator of depression liability would, therefore, relate conceptually and empirically to aberrant reward responsiveness, show greater associations with persistent depressive problems than with transient

situation-bound depression, and predict later emergence of clinical depression in presymptomatic at-risk individuals. A neural response measure that varies continuously with degrees of depression proneness would be particularly valuable, given the growing emphasis in the mental health field on dimensional assessments of psychopathology (see, e.g., Kotov et al., 2017).

A neurophysiological measure that appears to meet these criteria is the RewP, a brain ERP that is elicited by feedback signaling gain (reward) as compared to loss outcomes in a choice-feedback task. The RewP shows traitlike properties in terms of robust internal split-half and test-retest reliabilities (Bress, Meyer, & Hajcak Proudfit, 2015; Levinson, Speed, Infantolino, & Hajcak, 2017), and prior research has consistently demonstrated reduced magnitude of RewP in individuals diagnosed with MDD (Foti, Carlson, Sauder, & Proudfit, 2014; Liu et al., 2014). Studies using combined EEG and fMRI measurement have demonstrated convergence between RewP and reward-related neural activity in brain regions including the striatum, medial prefrontal cortex, and mesocorticolimbic dopaminergic tracts (Becker, Nitsch, Miltner, & Straube, 2014; Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011). There is also direct evidence showing that attenuation of mesolimbic dopamine levels produced by injection of alpha-methylparatyrosine (an inhibitor of catecholamine biosynthesis) results in an increase in anhedonic symptoms (Hasler et al., 2008), while direct, deep-brain stimulation of mesolimbic brain areas has been shown to decrease anhedonic symptoms in treatment-resistant depressed patients (Bewernick, Kayser, Sturm, & Schlaepfer, 2012).

Additionally, recent work linking heritable stress-response dysfunction with increases in melancholic depression provides support for the RewP as a viable neural indicator of persistent depressive illness; in a review on this topic, Pizzagalli (2014) posited that hypothalamic pituitary adrenal (HPA) axis dysregulation gives rise to downregulation of mesolimbic dopamine and an increase in anhedonic symptoms. Given evidence that the RewP is associated with activation of mesolimbic dopamine structures (Carlson et al., 2011), a reduction in this brain ERP response may serve as an index of persistent and severe depressive illness.

Also consistent with the idea that the RewP indexes a distinct liability factor for depressive symptomatology (i.e., low reward responsiveness), work by Bress, Foti, Kotov, Klein, and Hajcak (2013) has shown that blunted RewP in adolescent girls specifically predicts development of MDD in later life—but not anxiety disorders, which are often comorbid with MDD. In other work, Nelson, Perlman, et al. (2016) reported evidence that the predictive relationship of RewP with later MDD is independent of other prominent risk factors such as maternal history of depression and early depressive symptoms. Taken together, these lines of evidence suggest that low reward responsiveness as indexed by reduced RewP may represent a specific risk factor for persistent and severe depression.

1.3 | Present study

The present study was undertaken to evaluate the utility of a neurophysiological measure of reward responsiveness, the RewP, for indexing persistent depressive illness—as a step toward a neurobehavioral trait model (cf. Patrick, Durbin, & Moser, 2012; Venables et al., 2018; Yancey, Venables, & Patrick, 2016) for depression proneness. Specifically, we evaluated whether the RewP would relate more strongly to persistent depressive illness (as indexed by symptoms of dysthymia and depressive personality) than to current-episode depression, and whether a composite of the RewP and persistent depressive symptomatology would show convergent validity with respect to other diagnostic indicators of depression proneness (severity and recurrence of depressive episodes) and discriminant validity with respect to fear-related conditions (i.e., phobias and panic disorder).[1] Specific study hypotheses were as follows:

1. The difference in brain response to gain versus loss that defines the RewP will relate negatively to persistent depressive symptoms to a significant degree, and this association will account for any corresponding relationship with current depressive symptomatology.
2. Both persistent depression and current-state depression will show positive associations with fear-related disorders, consisting of specific phobia, social phobia, agoraphobia, and panic disorder (Krueger, 1999; Vaidyanathan et al., 2011).
3. A neuroclinical index (cf. Kwako, Momenan, Litten, Koob, & Goldman, 2016) consisting of persistent depressive symptoms combined with RewP response magnitude will operate as a "purer" index of a dimension of depression proneness compared to persistent depressive symptomatology alone—in terms of smaller magnitude associations with fear-related conditions but similar level associations with criterion measures of depression proneness (i.e., recurrence quantified as number of lifetime major depressive episodes [MDEs] and severity quantified as maximum level of MDD symptomatology experienced at any point in life).

[1]We tested for distinctiveness from fear-related conditions specifically, rather than internalizing conditions more broadly (i.e., fear and distress disorders; Krueger, 1999; Watson, 2005), because (a) distress disorders encompass major depression and dysthymic disorder, along with generalized anxiety disorder, which overlaps substantially with depression and dysthymia (Mineka et al., 1998); and (b) fear disorders appear more etiologically distinct from depression (Mineka et al., 1998; Venables et al., 2017).

2 | METHOD

2.1 | Participants

Participants were 201 adults (108 female; *M* age = 20.78, *SD* = 4.22), 36% of them individuals from the general community recruited via Craigslist and 64% undergraduates recruited from the population of a large public university through campus advertisements. Candidates for the study were prescreened for psychopathology-related traits (for details, see Strickland, Drislane, Lucy, Krueger, & Patrick, 2013) to enhance representation of clinical problems, including MDD, in the test sample. The racial/ethnic composition of the sample was as follows: 79% Caucasian, 12% African American, 5% Asian American, and 4% other including American Indian, Alaskan Native, and Hispanic/Latino.

Participants provided informed written consent prior to testing, and all study procedures were approved by the Institutional Review Board of Florida State University. Participants received either course credit or $10 per hr compensation for participating in the study.

2.2 | Self-report and diagnostic measures

2.2.1 | Persistent depression

Persistent depressive illness was operationalized in terms of symptoms of dysthymic disorder (dysthymia) and depressive personality disorder (PD), assessed using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; First, Spitzter, Gibbon, & Williams, 2002) and the Structured Clinical Interview for DSM-IV Axis II disorders (SCID-II; First, Spitzter, Gibbon, Williams, & Benjamin, 1994), respectively. Diagnostic interviews were conducted by advanced clinical psychology graduate students, and, in line with prior published work of this type (e.g., Iacono, Carlson, Taylor, Elkins, & McGue, 1999; Nelson, Strickland, Krueger, Arbisi, & Patrick, 2016), symptom ratings for DSM-IV disorders were assigned through a clinical consensus process overseen by a clinically trained academic psychologist (C.J.P.). Criteria for each disorder symptom were rated on a 3-point scale (i.e., *absent*, *subthreshold*, *present*).

Symptoms of dysthymia and depressive PD were used to index persistent depression because these conditions entail early emerging and more temporally enduring depressive tendencies. Symptom count scores were computed as the number of symptoms rated as present for each (maximum possible symptoms = 8 for dysthymia, 7 for depressive PD). Within the study sample of 201 participants, 84 (41.8%) exhibited at least one symptom of either dysthymia or depressive PD; Table 1 presents overall sample descriptive statistics (*M*s, *SD*s, ranges) for these symptom count scores, and online supporting information Table S1 presents descriptives by participant subsample (undergraduates, community adults). Symptom counts for these two conditions were standardized (*z* scored) and averaged together to form a persistent depression symptom score.

TABLE 1 Descriptive statistics for diagnostic measures in overall study sample

	M	*SD*	Range
Persistent and current-state depression measures			
Dysthymia symptom count*	0.44	1.48	0–7
Depressive PD symptom count	0.81	1.46	0–7
Current MDE symptom count	0.40	1.33	0–8
Beck Depression Inventory score*	8.39	8.25	0–47
Diagnostic criterion measures			
Depression proneness indicators			
Most severe MDE symptom count*	2.50	2.99	0–10
Number of MDEs (lifetime)*	0.44	2	0–2
Fear disorder symptom measures			
Specific phobia symptom count	1.37	2.08	0–9
Panic disorder symptom count	0.68	2.23	0–11
Agoraphobia symptom count	0.06	0.31	0–2
Social phobia symptom count	1.05	1.71	0–5

Note. See Table S1 of online supporting information for descriptive statistics by participant sample. PD = personality disorder; MDE = major depressive episode. $N = 201$.

*Significant ($p < 0.05$) difference between participant subsamples (community > undergraduate, in each case).

2.2.2 | Current depression

Current depression was quantified in two ways: (a) as current diagnostic symptoms of MDD, from among the 10 criteria for MDD assessed by the SCID-I interview protocol; and (b) as self-reported depressive tendencies, assessed using the revised form of the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996), a widely used 21-item measure that asks about depressive symptoms and affiliated features within the past 2 weeks (maximum possible score = 63). These two measures were standardized (*z* scored) and averaged to yield an aggregate index of current depressive symptomatology. This current depression variable showed a moderate-level correlation ($r = 0.48$, $p < 0.001$) with the above-noted persistent depression variable. Descriptive statistics for current depression symptoms are presented in Table 1 (for the overall study sample) and supporting information Table S1 (for undergraduate and community subsamples separately).

2.2.3 | Fear disorders

Symptoms of specific phobia, social phobia, agoraphobia, and panic disorder were also assessed using the relevant modules of the SCID-I. Mean symptom counts for these four conditions (maximum possible values = 10, 5, 2, and 16, respectively) among current study participants are presented for the overall study sample and for undergraduate/community subsamples in Table 1 and in Table S1, respectively.

2.2.4 | Criterion measures of depression proneness: Recurrence and severity

As mentioned in the Introduction, Klein and Kotov (2016) identified a qualitatively distinct subgroup of depressed individuals exhibiting chronic symptoms and poorer psychosocial functioning across time. This subgroup was characterized by greater recurrence of depressive episodes and more severe symptomatology during depressive episodes. Based on this work, we utilized the number of lifetime MDEs experienced by each participant as one criterion measure of depression proneness. This variable was quantified trichotomously, as follows: participants who had never met criteria for a full major depressive episode ($n = 147$) were assigned a score of 0, those who had experienced one full episode ($n = 27$) were assigned a score of 1, and those who had experienced two or more full episodes ($n = 27$) were assigned a score of 2. In addition, we used symptoms of the most severe depressive episode experienced by each participant over his/her lifetime as a second criterion measure of depression proneness. Descriptive statistics for these two measures, within the study sample as a whole and in undergraduate/community subsamples, are presented in Table 1 and Table S1, respectively.

2.3 | Experimental stimuli and design

The task procedure used to assess RewP response was a standard choice-feedback task used extensively in prior work (Proudfit, 2015). In the task, participants viewed a series of 40 pairs of doors and were instructed, on each trial, to choose either the left or the right door. Following the choice, an interstimulus interval of 1,000 ms occurred, after which either a positive feedback cue (green arrow pointing up, denoting reward of 50 cents) or a negative feedback cue (red arrow pointing down, denoting loss of 25 cents) appeared for 2,000 ms; the magnitude of reward was set to twice that of nonreward because evidence indicates that losses are valued twice as much as gains (Tversky & Kahneman, 1992). Participants were rewarded on exactly half of the task trials to control for the impact of probability on ERPs to gain versus loss feedback.

2.4 | Physiological data recording and reduction procedures

Data collection was performed using two IBM compatible computers, one running E-Prime presentation software (MEL Software, Inc.) for stimulus delivery, and the other running Acquire (Neuroscan, Inc.) software for physiological data acquisition. Raw EEG activity was recorded using a 128-channel elastic head cap (Neuroscan Quik-Cap) containing sintered Ag-AgCl scalp electrodes, positioned according to Neuroscan's nonstandard layout (NSL) system. Additional electrodes were placed above and below the left eye to measure vertical electrooculographic (EOG) activity and adjacent to the outer canthi of the left and right eyes to measure horizontal EOG activity. All electrode impedances were kept below 10 kOhms.

EEG signal activity was recorded using an online reference placed at the vertex of the scalp. An online bandpass filter of 0.05–200 Hz was used prior to digitization at 1,000 Hz. Following testing, the EEG data were rereferenced offline to the average of the left and right mastoid electrode sites. Data epochs from −1,000 ms to 2,000 ms were extracted from the continuous EEG recordings using EDIT version 4.5 software (Neuroscan, Inc.). Epochs were corrected for eye movements using an algorithm developed by Semlitsch, Anderer, Schuster, and Presslich (1986). Epoched and corrected EEG data were then imported into MATLAB (Mathworks, Inc.) for subsequent data processing.

Using MATLAB, the epoched EEG data were downsampled to 128 Hz, with application of an antialiasing filter. Trials on which signal activity exceeded ±75 μV during either the pre- (−1,000 ms − 0 ms) or poststimulus (0–2,000 ms) interval were excluded from processing. Data for excluded electrodes were interpolated using the mean activity from neighboring scalp sites. Trial epochs were averaged within gain and loss conditions separately. ERP scores were derived separately for each feedback condition from within a time window of 200–350 ms following feedback onset. Mean activity across a prestimulus baseline period extending from −200 to 0 ms was subtracted from all data points within the target time window. Topographic maps of grand averages for all scalp sites across all participants within this time window revealed maximal activation at NSL electrode 63, corresponding to the midline central (Cz) scalp site.[2] For each participant, two ERP score variables were computed for use in analyses, one reflecting the mean amplitude for loss trials within this time window (Spearman-Brown corrected split-half reliability = 0.90) and the other mean

[2]The mean number of unusable trials for electrode 63 (Cz analog) across all participants was 1.9 out of a total of 40 trials ($SD = 3.11$). Interpolation was performed for this electrode in only one case—using the mean of electrodes 62 and 64, each of which had zero unusable trials in this case.

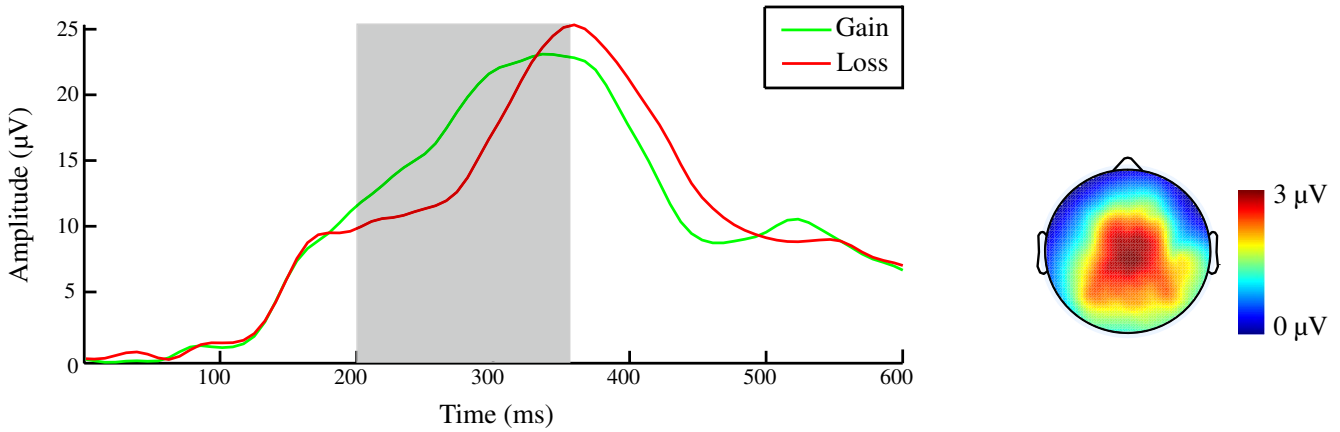

FIGURE 1 ERP waveforms for gain and loss trials of choice-feedback task at NSL electrode site 63 (akin to 10-20 site Cz). Gray region of the waveform plot represents the time window used for the reward positivity (RewP). Topographical map depicts the scalp distribution of the RewP difference score, which was maximal at frontocentral electrode sites

amplitude for gain trials (corrected split-half reliability = 0.89). The mean loss-amplitude score was then subtracted from the mean gain-amplitude score for each participant to yield the RewP score (corrected split-half reliability = 0.36; cf. Bress, Meyer, & Hajcak Proudfit, 2015). RewP scores were lower on average for the adult community portion of the study sample than for the undergraduate portion of the sample (*M*s/*SD*s = 3.53/2.20 and 4.21/3.95, respectively, $t(199) = -2.21$, $p = 0.03$).

2.5 | Data analysis

Separate mixed-model repeated measures analyses of variance (ANOVAs) were used to test for associations of RewP with persistent depression and current-state depression. Each ANOVA included a within-subject feedback factor representing gain and loss, along with either persistent depression or current depression score as a continuous between-subjects factor (to test the first and second parts, respectively, of Hypothesis 1). As a supplement to these analyses, a regression analysis utilizing the two depression variables as joint predictors was used to test the hypothesis that persistent depression would account for any observed association of current depression with RewP.

Bivariate correlations (Pearson's *r*s) were computed to quantify associations of persistent depression and current depression scores with fear disorder symptoms (Hypothesis 2) as well as with number of lifetime MDEs (coded as 0, 1, or 2) and maximum depressive episode severity (i.e., symptom count for most severe MDE experienced by each participant over his/her lifetime). Given the large proportion of zero values in these clinical criterion measures, Spearman rank (ρ) correlations are reported along with *r* coefficients. Lastly, in order to test Hypothesis 3, persistent depression scores and RewP response scores (i.e., gain-loss difference values, reversed to make higher scores indicative of reduced reward responsiveness) were each standardized and then averaged together to form a neuroclinical index of depression proneness. Correlational analyses were then performed to evaluate associations for this neuroclinical depression measure. Follow-up analyses using Steiger's *z* statistic were used to test for differences in associations (*r*s) for the neuroclinical composite with these clinical criterion measures relative to the persistent-depression symptom variable alone.

3 | RESULTS

3.1 | Brain response to feedback stimuli: Gain versus loss effect (the RewP) and relations with persistent and current depression

Replicating past research, a highly robust main effect of feedback type was evident, $F(1, 200) = 105.67$, $p < 0.001$, with an enhanced positive-going ERP deflection evident within the 200–350 ms time window following gain feedback (*M* waveform amplitude = 18.95 μV, *SD* = 7.75) compared to loss feedback (*M* = 15.93 μV, *SD* = 7.00). Waveforms and topographic maps depicting this gain versus loss trial (RewP) effect are displayed in Figure 1.

Also consistent with prediction, a significant Persistent Depression × Gain/Loss interaction was observed, $F(1, 199) = 8.758$, $p = 0.003$, reflecting reduced gain-loss differentiation (RewP) for individuals scoring higher on the persistent-depression symptom variable (see Figure 2).[3] By contrast, an

[3] A supplemental regression analysis including ERP amplitude scores for gain and loss trials as separate predictors of persistent depression was conducted to evaluate contributions of each to the difference score association. This analysis revealed significant associations, in opposing directions, for persistent depression with gain and loss trials: *B*s = −0.37 and 0.40, respectively, *p*s = 0.005 and 0.003. The implication is that persistent depressive symptomatology was associated with a general reduction in cortical-response differentiation between gain and loss outcomes, attributable both to decreased positive-going response to gain feedback and decreased negative-going response to loss feedback.

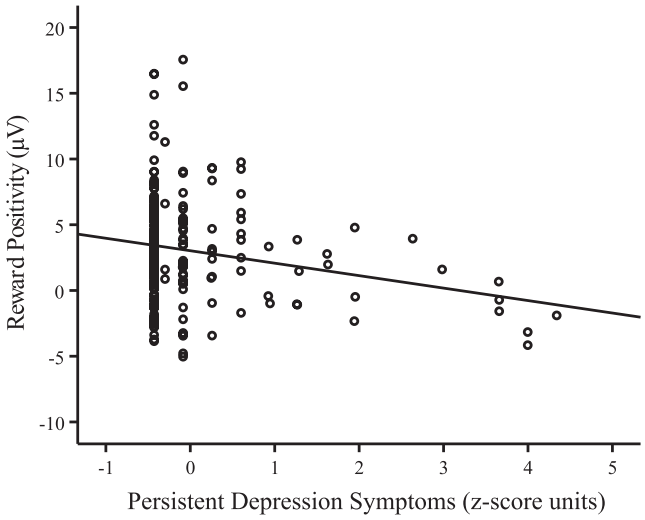

FIGURE 2 Scatterplot of relationship between reward positivity at NSL electrode site 63 (akin to 10-20 site Cz) and persistent depression symptom scores. Reward positivity is computed as the difference in brain response for gain as compared to loss trials in the choice-feedback task; persistent depression scores are computed as the average of standardized symptom counts for dysthymic disorder and depressive personality disorder

ANOVA including current depressive symptomatology (average of BDI and current MDD symptoms) along with feedback type (gain vs. loss) as between- and within-subjects factors, respectively, yielded no evidence of a Current Depression × Gain/Loss interaction, $F(1, 199) = 0.26$, $p = 0.61$. When both current depression and persistent depression were entered together in a regression model predicting RewP, persistent depression evidenced significant prediction ($\beta = -0.24$, $p = 0.003$), whereas current depression did not ($\beta = 0.08$, $p = 0.315$). Though broadly consistent with Hypothesis 1, the absence of any association of current depressive symptomatology with RewP is somewhat unexpected given its moderate-level association (as noted above) with persistent depression.

3.2 | Persistent depression and RewP: Associations with fear disorder symptoms and criterion measures of depression proneness

Consistent with Hypothesis 2, persistent depression (i.e., dysthymic/depressive-PD) symptom scores showed significant correlations with symptoms of fear-related disorders, though of somewhat lower magnitude on average than with the two criterion measures of depression proneness (recurrence quantified as number of lifetime MDEs and severity quantified as maximum depressive episode severity; see Table 2, second column from the right). Additionally, in line with Hypothesis 3, a neuroclinical index of depression proneness consisting of persistent depressive symptoms

TABLE 2 Reward positivity brain response, persistent depression symptoms, and neuroclinical depression composite: Relationships with diagnostic criterion measures

Diagnostic criterion measure	Reward positivity (RewP)	Persistent depression symptoms	Neuroclinical depression composite
Depression proneness indicators			
Number of lifetime MDEs	−0.13/−0.14*	0.32**/0.30**	0.26**/0.28**
Maximum MDE severity (lifetime)	−0.13/−0.15*	0.49**/0.46**	0.33**/0.40**
Fear disorder symptoms			
Specific phobia	0.06/0.08	0.19**/0.12	0.05/0.03[a]
Social phobia	0.07/0.01	0.36**/0.29**	0.12/0.18*[a]
Panic disorder	−0.04/−0.02	0.28**/0.35**	0.15*/0.24**[a]
Agoraphobia	0.06/0.04	0.22**/0.17*	0.04/0.09[a]
Overall fear symptoms	0.06/0.03	0.39**/0.35**	0.13/0.21**[a]

Note. Correlations with diagnostic criterion measures (depression proneness indicators, fear-disorder symptoms) are reported as Spearman's ρ/Pearson's *r*. Number of lifetime MDEs = number of major depressive episodes occurring within a participant's lifetime (coded as 0 = none, 1 = one, and 2 = two or more); reward positivity (RewP) = difference in brain response for gain versus loss trials in the choice-feedback task; persistent depression symptoms = average of standardized symptom counts for dysthymic disorder and depressive personality disorder; neuroclinical depression composite = average of standardized scores for RewP variable (reversed) and persistent depression symptom variable; maximum MDE severity (lifetime) = symptom count for maximally severe depressive episode experienced by participant during his/her lifetime.

[a]Correlation coefficient for neuroclinical depression composite score with clinical criterion measure is significantly lower (per Steiger's *z* statistic, using $p < 0.05$ significance threshold) than coefficient for persistent depression symptom score. *$p < 0.05$ **$p < 0.01$.

combined with (reversed scored) RewP showed comparable-level associations with the two criterion measures of depression proneness but significantly lower associations with fear-disorder symptomatology, as determined by Steiger's (1980) *z* statistic (see Table 2, right-most column). These selective reductions in associations with fear disorders reflect the fact that the RewP correlated only weakly/nonsignificantly with these disorders (and in a positive, though nonsignificant, rather than negative direction with specific and social phobia), whereas it correlated to a robust negative degree with number of lifetime MDEs and maximum depression severity (see Table 2, second column from left).

4 | DISCUSSION

The major aim of the current work was to demonstrate the utility of a conceptually relevant neurophysiological indicator for characterizing a dispositional dimension of depression proneness and distinguishing it from susceptibility to nondepressive forms of internalizing psychopathology (i.e., fear disorders). MDD is among the most common psychiatric disorders but has been shown to be phenotypically and etiologically heterogeneous. One variant of MDD, early onset persistent depression, has been linked to a more chronic disorder course and greater symptom severity, including heightened potentiality for suicide (Harrington et al., 1994). Our results suggest that the use of a continuous neural indicator of sensitivity to reward—the RewP brain response—can be helpful for indexing the dispositional susceptibility toward this more debilitating form of depression. More broadly, the current work provides a step in the direction of a neurobehavioral trait conceptualization (model) for depression proneness—akin to models being developed for neurobehavioral constructs of threat sensitivity (fear-fearlessness; Yancey et al., 2016) and inhibitory control (inhibition-disinhibition; Venables et al., 2018).

Consistent with previous published work (Proudfit, 2015), we found RewP response to be negatively related to clinical depression. However, the current work is the first to demonstrate specificity of this relationship to persistent depression, defined by symptoms of more temporally enduring depressive conditions (i.e., dysthymic disorder, depressive personality disorder) as opposed to current episode depression. Of note, a prior study by Bress, Smith, Foti, Klein, and Hajcak (2012) reported a negative association between RewP response and depressive symptomatology as indexed by the Children's Depression Inventory (CDI; Kovacs, 1992) in a young (8- to 13-year-old) participant sample. The CDI uses a past 2-week time frame in evaluating for depressive symptoms, so the depression assessment in this study might be viewed as current. However, given that persistent depressive illness is characterized by early age of onset, it could alternatively be the case that young participants attaining higher CDI depression scores in this study were primarily those with this form of depression.

Though the current investigation did not systematically assess for age of onset of depressive symptomatology, two other indices of depression proneness that were available for current study participants—number of lifetime MDEs (indicative of recurrence) and maximum level of MDE symptomatology experienced (indicative of depression severity)—covaried with RewP response as well as with persistent depression scores (in negative and positive directions, respectively). Research by Klein and Kotov (2016) has characterized a chronic, traitlike subtype of depression marked by enhanced recurrence and increased severity of depressive episodes. Our findings for these criterion measures lend support to the idea that blunted RewP response constitutes a neural marker of dispositional liability for depression (Proudfit, 2015) as opposed to a corollary of current depressive state.

Other published work provides additional support for this view. Kujawa, Hajcak, Proudfit, and Klein (2014) reported blunted RewP response in the asymptomatic young (age 9) children of mothers with a history of MDEs, pointing to reduced neural sensitivity as an indicator of dispositional risk for depression. Even more compellingly, other research has shown that reduced RewP prospectively predicts the later emergence of MDE in adolescent females without a history of clinical depression, when controlling for the presence of any current depressive tendencies (Bress et al., 2013; Nelson, Perlman, et al., 2016). Additionally, some work points to anhedonic tendencies as a neuropsychological substrate for the liability indexed by RewP. Foti et al. (2014) presented evidence that reduced RewP is particularly evident in depressed individuals who exhibit impaired mood reactivity to positive events (i.e., melancholic tendencies)—both in terms of reported experience and ventral-striatal reactivity to reward outcomes in a neuroimaging task.

In neuropsychological process terms, reward-sensitivity can be parsed into three distinct components—liking, wanting, and reward learning (Berridge, Robinson, & Aldridge, 2009). Neuroimaging studies that have examined functional brain correlates of the RewP provide some insight into which component of reward processing the RewP most reflects. An initial source-localization study by Foti, Weinberg, Dien, and Hajcak (2011) identified the putamen, a brain structure implicated in behavioral adjustments to reward outcomes (Wrase et al., 2007), as one probable source of the RewP. More direct evidence linking the RewP to the integration of hedonic reward valuation with action outcomes comes from a study demonstrating that the RewP is not elicited if feedback is delayed by a few seconds following performance of the relevant action (Weinberg, Luhmann, Bress, & Hajcak,

2012).[4] Given these findings, it seems likely that reduced RewP may reflect a reduced capacity for reward learning and that individuals with persistent depression may be characterized by impaired reward-learning capacity. While further research is needed to clarify what specific reward process the RewP most reflects, it appears that reduced RewP has utility for identifying both symptomatic and presymptomatic individuals with persistent depression.

Importantly, the present study also provides evidence that the use of RewP in conjunction with symptom indicators of depression can provide an index of depression proneness with good convergent validity and improved discriminant validity. Relative to symptoms alone, the composite index of depression incorporating RewP response (reversed) along with persistent depressive symptoms showed significantly lower associations with fear-disorder symptom scores while maintaining comparable associations with indices of depression recurrence and severity. The implication is that indexing a dimension of depression proneness in part based on a neural measure of reward sensitivity increases its distinctiveness from focal fear conditions. The fact that depression proneness defined in this way remained somewhat correlated with fear-disorder symptomatology may reflect a remaining shared element of negative affectivity between the two (Clark & Watson, 1991). In other work, we have operationalized a neurobehavioral trait dimension of threat sensitivity (or fear-fearlessness; Yancey et al., 2016) that relates substantially more to fear-disorder symptomatology than depressive symptomatology—etiologically as well as phenotypically (Venables et al., 2017). Considering this work together with current study findings, it is quite conceivable that further separation between dimensions of depression proneness and fear-disorder proneness could be achieved by quantifying both in joint psychological/neurophysiological terms.

To follow up on the preceding point, we do not consider a symptom-based neuroclinical composite to be the end goal of this work. Instead, our goal is to "bootstrap" (Cronbach & Meehl, 1955) from demonstrating a relationship between persistent depressive symptomatology with RewP to identifying other indicators in the psychological domain (i.e., items or questions) that capture an individual difference characteristic that relates both to persistent depressive symptomatology (prospectively as well as concurrently) and to RewP and other physiological indicators of reward sensitivity. That is, the aim is to conceptualize and measure a latent attribute of depression proneness utilizing indicators from both psychological scale and physiological response (and potentially also task behavioral) modalities of assessment. (For a detailed illustration of this multimethod approach as applied to the assessment of dispositional liability for externalizing disorders, see Venables et al., 2018). The reason it is important to use psychological scale items in conjunction with neural indicators is because this greatly enhances predictive relations with clinical outcome measures.

Some limitations of the present study are important to acknowledge. One is that the participant sample consisted of undergraduate students and adults from the general community rather than clinic patients. While participants were prescreened to enhance rates of psychopathology, only a portion of the sample (42%) exhibited some level of depressive symptomatology, and this relatively low level of depressive symptomatology constitutes a limitation of the study. Further research with samples exhibiting greater prevalence and severity of depressive symptomatology (e.g., community samples prescreened for persistent depressive symptoms, outpatient community samples) is needed to corroborate the current study findings and further explore their implications. In particular, it will be important to evaluate whether the association of RewP with persistent depressive symptomatology is evident in treatment-seeking individuals and to further evaluate its convergent validity in relation to early onset, persistent depression and its discriminant validity in relation to focal fear conditions and other psychiatric disorders. In addition, the age range of current study participants was somewhat restricted, given that an appreciable portion of the sample consisted of university students. Further research with older as well as younger participants will be needed to establish the generalizability of our findings. The purely cross-sectional nature of the present study is also a limitation. While some published longitudinal work exists on RewP as an indicator of depression liability, additional work of this kind is needed to confirm its distinct relationship to chronic depressive illness marked by anhedonic tendencies.

Notwithstanding these limitations, the current findings have important implications for research and, potentially, clinical assessment. MDD is a heterogeneous condition with multiple etiologic sources, and thus it is important to develop alternative assessment methods that address this heterogeneity. Given growing emphasis in the field on dimensional conceptualization and measurement of mental health problems (e.g., Kotov et al., 2017), a dimensional approach to assessing dispositional proneness to depression is likely to be of particular value. The current work illustrates the potential value of a neuroclinical approach (Kwako et al., 2016) for more effectively quantifying a dimension of depression proneness. From a research standpoint, the use of

[4]At the suggestion of an anonymous reviewer, we undertook exploratory analyses of relations of individual symptoms of persistent depression with RewP response in an effort to gain psychological insight into the nature of the individual difference characteristic accounting for the association between the two. Consistent with the idea that RewP indexes a process related to hedonic reward valuation, the symptoms that accounted most for the relationship between persistent depression and RewP were symptoms indicative of core affective-anhedonic symptoms of dysthymic disorder (i.e., symptoms pertaining to persistent depressed mood, lack of energy, low self-esteem, and feeling hopeless). Details of these analyses are reported in the final section of the online supporting information.

neurophysiological indicators together with symptom variables to define depressivity can provide improved phenotypic targets for brain and genomic investigations. For example, as shown by Foti et al. (2014), depression that is associated with anhedonic/melancholic symptoms and reduced RewP response links most clearly to aberrant reward-circuit reactivity. From a clinical standpoint, neurophysiological indicators may allow for early presymptomatic identification of at-risk individuals (Bress et al., 2013; Kujawa et al., 2014) who are likely to benefit most from prevention programs. Additionally, use of combined neurophysiological/symptom assessments with currently depressed patients may help to inform decisions about treatment (e.g., choice of direct brain stimulation vs. cognitive-behavioral interventions). Given the recent call from the American Psychiatric Association for proposed revisions to the DSM-5 diagnostic system (see https://www.psychiatry.org/psychiatrists/practice/dsm/submit-proposals), in which the use of biological markers is highlighted as a specific priority, the time appears ripe to move toward alternative neuroclinical methods for assessing dispositional liability to depression and other psychiatric conditions.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1

Table S1

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