HHS Public Access

Author manuscript

J Mood Anxiety Disord. Author manuscript; available in PMC 2023 November 17.

Published in final edited form as:

J Mood Anxiety Disord. 2023 October ; 3: . doi:10.1016/j.xjmad.2023.100025.

Characterizing positive and negative valence systems function in adolescent depression: An RDoC-informed approach integrating multiple neural measures

Kaylin E. Hill[*],
Samantha Pegg,
Anh Dao,
Emma Boldwyn,
Lindsay Dickey,
Lisa Venanzi,
Alexandra Argiros,
Autumn Kujawa

Department of Psychology and Human Development, Vanderbilt University, USA

Abstract

Depression is a prevalent, debilitating, and costly disorder that often manifests in adolescence. There is an urgent need to understand core pathophysiological processes for depression to inform more targeted intervention efforts. The Research Domain Criteria (RDoC) Positive Valence Systems (PVS) and Negative Valence Systems (NVS) have both been implicated in depression symptomatology and vulnerability; however, the nature of NVS alterations is unclear across studies, and associations between single neural measures and symptoms are often small in magnitude and inconsistent. The present study advances characterization of depression in adolescence via an innovative data-driven approach to identifying subgroups of PVS and NVS function by integrating multiple neural measures (assessed by electroencephalogram [EEG]) relevant to depression in adolescents oversampled for clinical depression and depression risk based on maternal history (N = 129; 14–17 years old). Results of the k-means cluster analysis supported a two-cluster solution wherein one cluster was characterized by relatively attenuated reward and emotion responsiveness across valences and the other by relatively intact responsiveness. Youth in the attenuated responsiveness cluster reported significantly greater depressive symptoms and were more likely to have major depressive disorder diagnoses than youth in the intact responsiveness cluster. In contrast, associations of individual neural measures with depressive symptoms were non-significant. The present study highlights the importance of innovative neuroscience approaches to characterize emotional processing in depression across domains, which is imperative to advancing the clinical utility of RDoC-informed research.

[*]Correspondence to: Department of Psychology and Human Development, Vanderbilt University, Peabody College #552, 230 Appleton Place, Nashville, TN 37203–5721, USA. kaylin.hill@vanderbilt.edu (K.E. Hill).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.xjmad.2023.100025.

Keywords

Depression; Adolescence; Positive valence; Negative valence; Event-related potentials

General scientific summary

This study suggests that depression in adolescence may be characterized by blunted neural function in positive and negative valence systems. Further, statistical approaches which leverage multiple neural measures may be more informative in characterizing functioning than any single neural measure in isolation.

Introduction

Depression is a prevalent, debilitating disorder and a leading cause of disability worldwide [1]. Rates of depression increase dramatically beginning around age 14 years and continue to increase through adolescence, with previous estimates suggesting 11–13% of youth experience a depressive episode by young adulthood [2,3]. Even more concerningly, severity of depression symptoms in adolescents has increased over the past decade [4], which is further compounded by an unprecedented two-fold increase in depression prevalence during the COVID-19 pandemic with a pooled prevalence estimate of 25.2% across 80,000 youth globally [5]. Early intervention is of paramount importance as adolescent depression is associated with profound difficulties across the lifespan, including high rates of recurrence, comorbid psychopathologies, widespread functional impairments, and elevated risk of suicidal thoughts and behaviors [6–8]. Yet, even our most effective interventions do not work for all youth with depression (e.g., [9]), and there is an urgent need to better understand core pathophysiological processes for depression to inform more targeted early intervention and prevention efforts.

Over the past decade, research informed by the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) framework has begun to characterize dimensions of emotion and cognition that underlie psychopathology and can be assessed across units of analysis (e. g., molecules, circuits, physiology, behavior; [10]). RDoC Positive Valence Systems (PVS) and Negative Valence Systems (NVS) domains have emerged as particularly relevant to depression. PVS is broadly responsible for actions and responses related to motivation, reward, and pleasure. In contrast, NVS drives responses in aversive contexts including loss and threat. Depression research has traditionally focused on NVS, given the core role of negative thoughts and emotions in longstanding theories of depression (e.g., [11]). However, altered NVS function underlies most forms of psychopathology, and there is growing evidence that low PVS function, including blunted reward responsiveness, may serve as a specific vulnerability for the later development of depression [12,13]. Further, although depression is characterized by high negative emotions [14], a more complex picture of NVS function in depression emerges across RDoC units of analysis. Born of observations across laboratory measures, the emotion context insensitivity (ECI) model suggests that despite a negative mood state, depression is characterized by reduced reactivity to both positive *and* negative environmental stimuli [15–17]. Support for the ECI model

is seen in a meta-analysis focused on self-report, behavioral, and peripheral physiological measures of emotional reactivity [15] and a growing body of work using neurophysiological measures [18]. Together, culminating evidence suggests that research examining RDoC units of analysis across both PVS and NVS are critical to moving the field forward in conceptualization of depression, particularly in adolescence—a period of development marked with increased onset and potential for intervention. Further, greater understanding of the distinct and overlapping roles of PVS and NVS function in adolescent depression is critical to refining current and developing new interventions for this population, particularly as dysfunction across systems is associated with different clinical features [19].

Electroencephalogram (EEG) methods are economical and accessible neural measures that can be applied to objectively assess emotional responses, and RDoC-informed research has begun to characterize the construct validity of EEG measures for assessing PVS and NVS function in depression (e.g., [20,13,21]). In particular, the reward positivity (RewP) and late positive potential (LPP) event-related potential (ERP) components are reliably elicited in response to reward feedback and salient emotional images, respectively [22,23]. Further, the RewP to rewards and LPP to emotional images correlate with individual differences in other facets of PVS/NVS function, including self-reported and observed affect [20,21,24]. The RewP is typically examined using monetary reward tasks and is characterized by a peak 250–350 ms after feedback onset over frontocentral sites that is enhanced for positive/reward relative to negative feedback [25]. Studies leveraging both EEG and neuroimaging methods indicate correlations between RewP and activation of reward circuits including medial prefrontal cortex (mPFC) and ventral striatum [26–28]. In addition to the initial response to reward captured by the RewP, more sustained processing of ecologically valid emotional stimuli can be reliably measured using the LPP component, which emerges approximately 300 ms after the onset of motivationally salient stimuli [29]. Combined EEG–fMRI studies indicate correlations between the LPP and visual cortex activation, along with PVS and NVS-related circuits including mPFC, amygdala, and insula [30,31].

Associations between depression and a reduced RewP to reward feedback and LPP to pleasant images have been observed across development (e.g., [32–36]), and even conceptualized as reflecting endophenotypes for depression [37], but effect sizes are modest and not always replicated [13]. Further, a more complex picture emerges when examining the LPP to negatively valenced stimuli. On one hand, there is evidence of an *attenuated* LPP to negative images in adults and adolescents with depression [38–41], but others have found a *potentiated* LPP to negative words [42,43]. This may be due to the personal relevance of task stimuli, as studies using self-referential tasks tend to demonstrate potentiated NVS responsiveness [42,44,43], while tasks using more general stimuli tend to demonstrate attenuated NVS responsiveness [38–41], but it could also be the result of other task differences (e.g., image versus word stimuli). Importantly, research using both the RewP and LPP in adults indicates that these components show *independent* associations with depression [45], supporting the need to integrate multiple neural measures to better characterize processes underlying depression.

In laboratory tasks, the function of PVS and NVS are typically measured using tasks that present monetary rewards or valenced but content nonspecific images. However, depression

is often characterized by impairments in social functioning, including lack of social motivation, social anhedonia, and impairments in social communication and perception, likely driven in part by alterations in PVS-related processes [46]. Further, interpersonal stress that disrupts reinforcers in the environment is one of the best-established predictors of depression, particularly among those with pre-existing tendencies towards low reward responsiveness [47–50]. This may be particularly relevant in adolescence, a developmental period of change in social motivations, including increased desires for peer acceptance [51–53]. To measure PVS and NVS in the social domain in the present study, we use two innovative tasks, which have demonstrably informed understanding of emotional processes in depression ([54,34,55–59]; Pegg, Ethridge, et al., 2019b). First, we use a real-time peer interaction task to elicit the RewP in response to peer acceptance feedback [60], with preliminary evidence that the social RewP is uniquely associated with depression beyond the monetary RewP (Pegg et al., 2021b). Next, to capture neural responses to more complex social processes, we developed and validated a set of pleasant and unpleasant interpersonal emotional images relevant to the real-world experiences of adolescents, which we demonstrated reliably elicit the LPP and capture alterations in emotional processing in depression [34,54]. Yet, we and others have generally considered these tasks and measures separately or tested the unique predictive validity of each, and advanced statistical models offer the opportunity to *integrate* information across measures, which may ultimately enhance their clinical utility in terms of characterizing symptomatology, identifying those most at risk, and matching individuals to interventions that best meet their needs.

Despite the promise of RDoC-informed approaches to characterizing psychopathology, several challenges remain. First, relatively modest effects are typically observed when linking single neural and physiological measures to symptom measures [61]. This may be due, in part, to the fact that self-report measures are confounded by shared method variance with symptom measures, which leads to overestimates of the true effect size. Second, recent research calls into question the ability to model latent variables for PVS and NVS assessed across units of analysis [62], which calls to question the current RDoC organization and theoretical framework. It may be that new approaches to leveraging multiple indicators of PVS and NVS function in depression research are needed for the next phase of RDoC-informed research and actualizing aims of increasing the translational impact of this research.

The goal of the current study was to leverage multiple neural measures to characterize PVS and NVS function in relation to adolescent depression. Specifically, we used an innovative cluster analysis approach in adolescents oversampled for clinical depression or depression risk based on maternal history of depression [63] to characterize groups of individuals that vary in PVS and NVS function. Cluster analysis is a data driven multivariate technique that empirically identifies groups of subjects by minimizing within-group variability (i.e., high intra-class similarity) while maximizing between-group variability (i.e., low inter-class similarity) through an iterative process (Hair & Black, 2000). We included multiple neural measures of PVS function (i.e., RewP to monetary reward, RewP to social reward, and LPP to pleasant interpersonal images) to examine the combined effects of these PVS components. We also included a neural measure of NVS function (i.e., LPP to unpleasant interpersonal images) to examine the generalizability of blunted responsivity

across the PVS/NVS domains or the extent to which distinct clusters for variability in NVS function emerged. Informed by the ECI model of depression, we hypothesized that two clusters would emerge wherein one cluster would be characterized by blunted responses across PVS/NVS measures and one cluster would be characterized by relatively intact responsiveness. Given that cluster analysis is a data-driven approach without a priori parameters related to theory, we also had an alternative hypothesis wherein three clusters would emerge, characterized by relatively attenuated PVS, relatively potentiated NVS, and relatively intact PVS and NVS neural function. Next, we examined the extent to which these clusters related to depressive symptoms and risk. In conjunction with our primary hypothesis informed by ECI, we hypothesized that adolescents in the cluster characterized by generalized blunted responsiveness would demonstrate more depressive symptoms. Alternatively, we hypothesized that in the case of a three-cluster solution, the two clusters characterized by attenuated PVS and potentiated NVS neural function would demonstrate more depressive symptoms than the cluster characterized by relatively average PVS and NVS neural function. We further hypothesized that cluster membership, which leverages multiple sources of data on brain function, would demonstrate stronger associations with depressive symptoms and risk than individual ERP components considered alone.

Method

Participants

Participants were recruited as part of a study of adolescents 14–17 years old with and without depressive disorders and at relatively high and low risk for depression based on maternal history of depression. A total of 165 participants were recruited for the present study; however, a portion of participants withdrew ($n = 2$) or did not have available EEG data (e.g., did not complete a task, too many artifacts for data extraction; $n = 10$ all tasks; $n = 6$ monetary reward task, $n = 11$ social reward task, $n = 7$ emotion task). A total of 129 participants (61.2% female; 58.1% identified as girls, 37.2% as boys, and 4.65% preferred to self-describe [i.e., gender fluid] or did not report) completed all components of the interview and EEG visit and were included in the present analyses. The sample had a mean age of 15.19 years ($SD = 1.09$). The sample was 5.4% Hispanic and/or Latine, 76.7% White/Caucasian, 10.9% Black and/or African American, 6.2% Asian, 1.6% Native Hawaiian and/or Pacific Islander, 0.8% American Indian and/or Alaska Native, and 3.9% identified as another race.

Three participants did not complete the self-report of depressive symptoms. Of participants included in analyses, 34.1% of participants were clinically depressed at the time of the study (i.e., major depressive disorder [MDD], persistent depressive disorder [PDD], or unspecified depression), 34.1% were at high risk for depression based on maternal history of depression (but had not yet experienced a depressive episode themselves), and 31.8% were considered relatively low risk for depression based on no personal or maternal histories of depression. Additionally, 17.05% of participants met criteria for current social anxiety disorder, 22.48% for generalized anxiety disorder, 0.78% for obsessive compulsive disorder, 2.33% for posttraumatic stress disorder, 6.20% for unspecified anxiety, 0.78% for adjustment disorder, 0.78% for binge eating disorder, 11.63% for attention deficit hyperactivity disorder, 0.78%

for ODD, 1.55% for unspecified DBD, 2.33% for substance use disorder, and 7.75% for other disorders. 20.93% of participants were in current outpatient treatment (n = 17 in therapy or counseling, n = 2 on medication only, n = 7 a combination of therapy and medication, and n = 1 did not report type).

The mothers of the adolescents included in the present study were 32–58 years old (M = 45.23, SD = 5.21). In terms of current depressive diagnoses, 3.1% met criteria for current MDD, 2.32% for current PDD, 2.33% for current MDD and PDD, and 1.55% for current unspecified depression. For past depressive diagnoses, 30.97% met criteria for past MDD, 3.87% for past PDD, 17,83% for past MDD and PDD,.78% for past other specified depression, and 9.3% for past unspecified depression. As such, 62.8% of mothers met criteria for lifetime clinical depression.

Procedure

The Vanderbilt University Institutional Review Board approved this study. Informed consent was obtained from all parents with assent obtained from minor participants. Following consent/assent, participants and their biological mothers were interviewed using semi-structured diagnostic interviews to determine diagnoses. Next, participants completed questionnaires assessing depressive symptoms and visited the laboratory for an EEG assessment, which included each of the tasks described below completed in a counterbalanced order. The median time between the diagnostic interview and EEG assessment was 14 days (*range*: 0–233 days; 93.8% completed within 2 months) and between symptom self-report and EEG assessment was 8 days (*range* = 0–155 days; 97.7% completed within 2 months). See supplemental materials.

Measures

Diagnostic interviews—The mood disorders module of the Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID; [64]) was used to determine diagnoses for mothers, and the DSM-5 version of the Schedule for Affective Disorders and Schizophrenia for School Age Children (KSADS; [65]) was administered for adolescent diagnoses. Interviews were administered by advanced graduate students under the supervision of a licensed clinical psychologist (AK). A second interviewer reviewed audiotapes for a subset of interviews (n = 15 KSADS, n = 14 SCID), and inter-rater reliability was excellent for both adolescent and mother diagnoses of depressive disorders (kappas=1.0).

Depressive symptoms—Depressive symptoms were measured using the Mood and Feelings Questionnaire (MFQ; [66]). The self-report 33-item MFQ assesses depressive symptoms in the past two weeks using a 3-point Likert scale. The MFQ had excellent internal consistency in the current sample (N = 126; 33 items; Cronbach's α = .96). Scores in the present sample ranged from 0 to 61 (M = 15.53; SD = 14.28).

Monetary reward task—Participants completed a simple guessing reward task (i.e., Doors) to measure monetary reward responsiveness [33,35]. This task is validated and widely used to examine neural reactivity to monetary rewards across development [55,58,25].

Social reward task—Participants completed the Island Getaway task ([60]b), which simulates social interactions between peers to measure neural responses to social acceptance and rejection feedback. Previous studies have shown that the task reliably elicits ERPs sensitive to social reward (i.e., peer acceptance feedback; [23,55]). The task code is available at: https://github.com/Kodiologist/Survivor/tree/vanderbilt.

Interpersonal emotional interrupt task—Participants completed a novel interpersonal emotion task [34,54] adapted from an established emotional interrupt paradigm, which has been shown to reliably elicit the LPP in prior research (e.g., [23,67]).

See supplemental materials for additional task details.

EEG data collection and processing—EEG data were continuously recorded using a 32-channel BrainProducts actiCHamp System and BrainVision Recorder software (Munich, Germany) with a 1000 Hz sampling rate and impedances below 30 kΩ. For a portion of participants (15.5%) who completed EEG assessments early in the COVID-19 pandemic, a subset of 16 key electrodes were collected on the 32-channel system to minimize time in close contact (as suggested by others, see [68]). Facial electrodes were attached approximately 1 cm above and below one eye and 1 cm on each outer corner of the eyes to measure electrooculogram and referenced to an electrode placed on the back of the participant's neck, per the BrainProducts bipolar-to-auxillary adapter design. EEG data were processed offline using BrainVision Analyzer software (Munich, Germany) and filtered from 0.1 to 30 Hz for RewP and 0.01–30 Hz for the LPP (due to evidence that a more stringent high pass filter attenuates later stages of the LPP; [69]). Data were re-referenced to the linked mastoids. Data were segmented from −200 ms before to 800 ms after stimulus onset for the monetary reward task and −200 ms before to 1000 ms after stimulus onset for the social reward and interpersonal emotional interrupt tasks. Data were corrected for eye movements using Gratton's algorithm [70]; for 16-channel assessments, eye movements were accounted for using channels FP1 for vertical eye movements and FT9/FT10 for horizontal eye movements. Artifacts were removed using semi-automated procedures, with the following criteria: maximal allowed voltage step: 50 μV/ms; maximal allowed difference of values in intervals: 175 μV (interval length: 400 ms); minimal allowed amplitude: −200 μV; maximal allowed amplitude: 200 μV; and lowest allowed activity in intervals: 0.5 μV (interval length: 100 ms). For the LPP, the minimal and maximal allowed amplitude parameters were not included in automated artifact detection, but additional artifacts were identified using visual inspection and removed for all participants and tasks.

Average ERPs were computed for each condition and baseline corrected to 200 ms preceding stimulus onset. See Fig. 1 for ERP waves and scalp distributions for each task. ERPs were scored based on prior literature ([34,54]; Pegg et al., 2021b; [71]) and visual inspection of the grand averaged data. Specifically, the monetary RewP was scored 250–350 ms after gain and loss feedback onset at Cz. The social RewP was scored 275–375 ms after acceptance and rejection feedback onset at Cz. The LPP was scored 400–1000 ms following positive, negative, and neutral image onset at a pooling of occipitoparietal sites (i.e., Pz, Oz, O1, O2). Notably, all participants had the channels necessary for these scoring procedures, whether 16 or 32 channels were collected during EEG recording. To isolate variability in the

ERP wave attributed to emotional processes, unstandardized residual scores were calculated using a linear regression for each task [72]. Specifically, the monetary RewP residual score was computed with response to wins partialing out response to losses. The social RewP residual score was computed with response to acceptance feedback partialing out response to rejection feedback. The positive LPP residual score was computed with response to pleasant interpersonal images partialing out response to neutral images. Similarly, the negative LPP residual score was computed with response to unpleasant interpersonal images partialing out response to neutral images. See supplemental materials for reliability estimates of ERP measures.

Data analysis—First, to derive groups of participants based on neural measures of emotionality, the four ERPs, together reflecting individual differences neural reactivity across monetary reward, social reward, positive emotional reactivity, and negative emotional reactivity domains, were entered into a cluster analysis. We classified individuals based on their neural reactivity profiles using *k*-means cluster analysis, a traditional machine learning method, using the *R* statistical software (R Core Team, 2022) with tidyverse [73], dbplyr [74], cluster [75], factoExtra [76], and factoextra [77] packages. All variables were standardized prior to cluster analysis. We initially set *k* (i.e., the number of clusters used to derive the solution) according to our a priori hypotheses of two distinct clusters. We also confirmed $k = 2$ as the optimal number of clusters using the elbow method [78] and Silhouette coefficient [79] methods to determine if a two- or three-cluster solution was more appropriate for the data.

Next, to examine the clinical significance of the derived clusters, we used *t*-test, chi-square, and kendall's tau b procedures in IBM SPSS Statistics for Windows Version 28.0 (IBM Corp, 2020) for examining associations with continuous symptoms and diagnostic or risk categories, respectively. We examined depression diagnoses according to (1) any depressive disorder (i.e., MDD, PDD, and unspecified depression) and (2) MDD specifically, given that anhedonia is exclusively a symptom of MDD. We used corrected values when the homogeneity of variance assumption was violated according to Levene's test. We then examined these associations amongst symptoms and diagnostic and risk categories with individual ERP components via correlational analyses (Pearson's *r*) to examine the utility of the cluster classification approach vs. associations with individual ERP components.

Data availability—Analysis code for cluster analyses is available at https://osf.io/8m6te/?view_only=685c16531b344f0791918c11b2d87d69. Data are available by request to the corresponding author. This study was not preregistered.

Results

Cluster Analysis to Characterize Patterns of PVS and NVS Function in Adolescents

Elbow and silhouette methods supported a two-cluster solution as best fitting the underlying structure of the data. The elbow method indicated decreased slope in the total within sum of squares after the two-cluster solution and the silhouette method indicated that two clusters had the largest average silhouette width (see Fig. 2). Cluster 1 included 86 adolescents and reflected relatively blunted reactivity across neural measures and valences (monetary RewP

M=−0.01, *SD*=0.96; social RewP *M*=− 0.16, *SD*=0.92; positive LPP *M*=− 0.50, *SD*=0.63; negative LPP *M*=− 0.47, *SD*=0.64). On the other hand, Cluster 2 included 43 adolescents and was characterized by relatively intact reactivity across neural measures and valence (monetary RewP *M*=.03, *SD*=1.09; social RewP *M*=0.37, *SD*=1.01; positive LPP *M*=0.96, *SD*=.83; negative LPP *M*=0.94, *SD*=.93; see Fig. 3. 4). This indicates that adolescents oversampled for depression and depression risk vary on PVS and NVS function across multiple neural measures, and that low NVS function, as measured by the LPP, appears to cluster with low PVS function. Given our strong a priori hypotheses with the derived 2-cluster solution, we used one-tailed significance testing for remaining analyses.

Associations between Cluster Membership and Individual ERPs

Bivariate associations are provided in Table 1. Social ERP components (i.e., social RewP, positive LPP, negative LPP) shared small to large positive, statistically significant associations, and the two LPP observations, to positive and negative social images respectively, shared the largest association. The single ERP measure examined outside of a social context (i.e., monetary RewP) was not statistically significantly associated with the other ERP measures. Similarly, cluster membership was significantly associated with the social RewP, positive LPP, and negative LPP, but not the monetary RewP. Cluster membership shared statistically significant, though small, bivariate associations with MDD diagnosis and self-reported depressive symptoms.

Associations between Cluster Membership and Depression Diagnoses and Risk

Chi-square analyses revealed that cluster membership was not significantly associated with adolescent depressive disorder diagnoses when considering MDD, PDD, and unspecified depression combined (χ^2=.43, one-tailed p = .325, V=.07[.01,.22]), but adolescents with MDD were over-represented in the blunted PVS/NVS function cluster (χ^2=3.63, one-tailed p = .029, V=.18[.04,.31]; statistical significance was trending with 2-tailed test, p = .057). Specifically, 26.74% of youth in Cluster 1 had MDD diagnoses, whereas only 13.95% in Cluster 2 had MDD. In contrast, no significant differences were observed between clusters for the distribution of maternal lifetime depression diagnoses (χ^2=.41, one-tailed p = .261, V=.08[.01,.23]).[1] See Fig. 5. Individual ERP components were not significantly associated with adolescent or maternal depression diagnoses, with the exception of the positive LPP sharing a small negative association with MDD (Table 1). Together, results suggest that adolescent depression, particularly MDD, is characterized by blunted NVS/PVS function at the neural level, although there is variability in diagnoses and risk status within each cluster.

Association between Cluster Membership and Depressive Symptom Severity

Independent samples *t*-test analyses revealed that depressive symptoms significantly differed by cluster (t(115.72) = 2.01, one-tailed p = .024, d= .33 [−.05,.70]; *t*-test remained significant with 2-tailed test, p = .047) such that symptoms were higher in the cluster with blunted PVS/NVS reactivity (Cluster 1; *M*=16.44, *SD*=14.90) relative to the group with intact PVS/NVS function (Cluster 2; *M*=12.07, *SD*=9.27). In contrast, individual

[1]Similarly, no significant differences were observed between clusters for the distribution of maternal current MDD diagnosis, χ^2 = .47, one-tailed p = .246, V= .06[.01,.21].

ERP components were not significantly associated with depressive symptoms (Table 1), supporting the utility of integrating multiple neural measures through approaches like cluster analysis.

Given that we tested 4 associations between cluster membership and depression measures, we also applied a False Discovery Rate correction and no associations remained significant (Benjamini-Hochberg adjusted p's > .088). Additionally, we evaluated associations with depression as a latent variable to reduce the number of tests, and cluster membership was significantly associated with the latent measure. See supplemental materials.

Discussion

The aim of the current study was to examine patterns of PVS and NVS neural function in adolescents oversampled for depression and depression risk. Extending beyond research on single measures, we leveraged multiple neural indicators across three validated EEG tasks, reflecting monetary reward responsiveness, social reward responsiveness, and positive and negative emotional reactivity. We found two distinct clusters of adolescents—one which was characterized by blunted responsiveness to rewards and *both* positively and negatively valenced emotional stimuli and one which was characterized by relatively intact responsiveness across domains. These results highlight the utility of cluster analyses to integrate information across measures and elucidate variability in PVS and NVS function. Further, supporting the ECI model of depression, the cluster characterized by general blunting of reward and emotional responses was associated with adolescent MDD diagnoses and depressive symptom severity. Critically, these associations were the most consistent across depressive measures when considering cluster membership rather than single ERPs, although effect sizes were relatively modest even for the cluster. Cluster membership was significantly associated with both MDD diagnosis and self-reported depressive symptoms, while associations amongst depression measures and individual ERPs were more varied. Specifically, the positive LPP shared a small, significant negative association with MDD diagnosis, and the negative LPP and social RewP demonstrated a similar pattern though statistically non-significant. Similarly, all ERPs showed a pattern of non-significant negative associations with self-reported depressive symptoms.

Social ERP components were interrelated, while the ERP measure examined outside of a social context (i.e., monetary RewP) was not significantly associated with the other ERP measures and was not associated with cluster membership. This could suggest that social neural processing may be particularly relevant to cluster membership in the present analysis with these tasks. It is notable, however, that the monetary RewP nonetheless shared the same pattern (dampened versus intact) across clusters. Our supplemental analyses also demonstrated that the ERPs included in the cluster analysis influence the number of clusters derived and the associations amongst clusters and depression symptoms, though the pattern of a relatively blunted cluster sharing a positive association with depression was consistent. Lastly, considerable variability in depression was observed in both clusters, potentially reflecting heterogeneity in depression. Together, these findings support neuroscience methods considering multiple measures in conjunction rather than in isolation both to inform RDoC research and theories of psychopathology.

Similar to prior work, we observed relatively modest associations between neural measures and depression (e.g., for a review, [13]). The small effect sizes, especially in the context of analyses across RDoC units of analysis, may be representative of true associations in the multimethod matrix [61,62]. That is, traditional clinical research relying on self-report measures may overestimate true effects due to shared measurement variance. Nonetheless, the lack of statistically significant bivariate associations between the monetary RewP and measures of depression in particular is notable and unexpected, though has also been observed in previous studies [e.g., [80–83]]. Given these inherent challenges of clinical neuroscience research, innovative tools are needed to increase the clinical utility of uncovering the processes involved in depression onset and vulnerability. This study uniquely leveraged a cumulative measure approach wherein patterns across PVS and NVS RDoC domains conferred cluster membership and cluster differences in depressive symptomatology according to self-reported severity and MDD diagnosis. Altogether, the associations between cluster and depressive symptomatology were still relatively modest in the present study, including loss of statistical significance when correcting for the False Discovery Rate and low specificity and sensitivity at the individual level. For example, if the cluster analysis were used to diagnose adolescents with depression from the present sample, the results suggest that the cluster analysis correctly grouped 79.31% of cases of MDD into Cluster 1. While this percentage is impressive for an initial inquiry, it is insufficient for clinical use. Future investigations could leverage similar approaches with multiple units of analysis within RDoC (e.g., circuit, physiology, behavior, self-report) to better leverage the clinical utility of multimethod data and improve specificity and sensitivity. Further, there are many approaches to ERP scoring methods, such as time-frequency decomposition [84,85], which could be considered in future research using machine learning approaches.

Inclusion of additional RDoC units may provide even greater characterization of depression symptomatology and risk. In particular, the current findings support the ECI model of depression in that blunted functioning across domains characterized the cluster associated with depression symptomatology [18]. It is possible this pattern of results is specific to our measure of NVS function, the LPP to threatening social images, and there is a need to consider other measures of NVS function in future work that might lead to a third cluster characterized by potentiated NVS function. For example, adolescents with depression may experience greater variance in negative affect in daily life, an effect captured by ecological momentary assessment [86]. Second, it is notable that most adolescents were in the blunted PVS/NVS cluster. This may reflect the strategized sample, wherein adolescents were oversampled for depression and depression risk. Future studies should examine if the clusters identified here replicate in community and clinical samples. Third, we examined patterns of neural responsiveness in relation to depression symptoms cross-sectionally. An exciting next step for this line of research is to leverage this innovative methodological approach to integrating multiple neural indicators for prospective prediction of symptom changes and treatment response across time. Our prior research indicates that individual differences in neural responses to rewards predict change in depressive symptoms with treatment [87,88], and approaches like cluster analysis may hold promise in leveraging multiple types of data to best predict treatment outcomes or depressive course over time. Further, this approach will advance not only understanding of depressive symptomatology,

but other comorbid or overlapping psychopathology and trajectories of development across time, including the oftentimes overlapping anxiety disorders.

In conclusion, we examined patterns of PVS and NVS neural function in adolescents oversampled for depression and depression risk and found that neural measures of reward and emotional reactivity—across domains and valences—together were associated with adolescent MDD diagnoses and depression symptoms, such that depression was most likely to be characterized by attenuated neural PVS and NVS function across measures. In contrast, single ERP components showed somewhat weaker and less consistent associations with depression measures. Future research is needed using machine learning approaches such as cluster analysis to not only inform current symptoms but predict prospective associations with symptomatology and treatment outcomes—thus, the current study serves as a foundation from which personalized medicine approaches informed by RDoC and clinical neuroscience research can build.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding and Declaration of Interests

This work was supported by a Brain and Behavior Research Foundation Katherine Deschner Family Young Investigator Grant and Klingenstein Third Generation Foundation Fellowship awarded to AK, as well as UL1 TR000445 from NCATS/NIH. KEH was supported by NIH T32 MH18921, SP by NIH T32 MH18921 and NIH F31MH127817, and LD by NIH F31 MH127863 during completion of this work. The authors do not have any competing interests to declare.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Autumn Kujawa reports financial support was provided by Brain and Behavior Research Foundation. Autumn Kujawa reports financial support was provided by Klingenstein Third Generation Foundation. Kaylin Hill reports financial support was provided by National Institutes of Health. Samantha Pegg reports financial support was provided by National Institutes of Health. Lindsay Dickey reports financial support was provided by National Institutes of Health.

References

[1]. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med 2013;10(11). 10.1371/journal.pmed.1001547.

[2]. Avenevoli S, Swendsen J, He J-P, Burstein M, Merikangas KR. Major depression in the national comorbidity survey–adolescent supplement: prevalence, correlates, and treatment. J Am Acad Child Adolesc Psychiatry 2015;54(1):37–44.e2. 10.1016/j.jaac.2014.10.010. [PubMed: 25524788]

[3]. Lu W Adolescent depression: national trends, risk factors, and healthcare disparities. Am J Health Behav 2019;43(1):181–94. 10.5993/AJHB.43.1.15. [PubMed: 30522576]

[4]. Twenge JM, Joiner TE, Rogers ML, Martin GN. Increases in depressive symptoms, suicide-related outcomes, and suicide rates among U.S. adolescents after 2010 and links to increased new media screen time. Clin Psychol Sci 2018;6(1):3–17. 10.1177/2167702617723376.

[5]. Racine N, McArthur BA, Cooke JE, Eirich R, Zhu J, Madigan S. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: a meta-analysis. JAMA Pediatr 2021;175(11):1142–50. 10.1001/jamapediatrics.2021.2482. [PubMed: 34369987]

[6]. Copeland WE, Alaie I, Jonsson U, Shanahan L. Associations of childhood and adolescent depression with adult psychiatric and functional outcomes. J Am Acad Child Adolesc Psychiatry 2020. 10.1016/j.jaac.2020.07.895.

[7]. Harrington R, Bredenkamp D, Groothues C, Rutter M, Fudge H, Pickles A. Adult outcomes of childhood and adolescent depression. III Links with suicidal behaviours. J Child Psychol Psychiatry 1994;35(7):1309–19. [PubMed: 7806612]

[8]. McLeod GFH, Horwood LJ, Fergusson DM. Adolescent depression, adult mental health and psychosocial outcomes at 30 and 35 years. Psychol Med 2016;46(7): 1401–12. 10.1017/S0033291715002950. [PubMed: 26818194]

[9]. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for adolescents with depression study (TADS) randomized controlled trial. JAMA: J Am Med Assoc 2004;292(7):807–20. 10.1001/jama.292.7.807.

[10]. National Institute of Mental Health. (2020). RDoC Matrix. http://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml.

[11]. Beck AT (1967). Depression: Clinical, Experimental and Theoretical Aspects. Hoeber.

[12]. Keren H, Callaghan GO, Vidal-Ribas P, Buzzell GA, Brotman MA, Leibenluft E, et al. Reward processing in depression: a conceptual and meta-analytic review across fMRI and EEG studies. Am J Psychiatry 2018;19:1–10. 10.1176/appi.ajp.2018.17101124.

[13]. Kujawa A, Burkhouse KL. Vulnerability to depression in youth: advances from affective neuroscience. Biol Psychiatry: Cogn Neurosci Neuroimaging 2017;2(1): 28–37. 10.1016/j.bpsc.2016.09.006.

[14]. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.).

[15]. Bylsma LM, Morris BH, Rottenberg J. A meta-analysis of emotional reactivity in major depressive disorder. Clin Psychol Rev 2008;28(4):676–91. 10.1016/j.cpr.2007.10.001. [PubMed: 18006196]

[16]. Rottenberg J. Mood and emotion in major depression. Curr Dir Psychol Sci 2005;14 (3):167–70. 10.1111/j.0963-7214.2005.00354.x.

[17]. Rottenberg J, Hindash AC. Emerging evidence for emotion context insensitivity in depression. Curr Opin Psychol 2015;4:1–5. 10.1016/j.copsyc.2014.12.025.

[18]. Bylsma LM. Emotion context insensitivity in depression: toward an integrated and contextualized approach. Psychophysiology 2021;58(2):e13715. 10.1111/psyp.13715. [PubMed: 33274773]

[19]. Medeiros GC, Rush AJ, Jha M, Carmody T, Furman JL, Czysz AH, et al. Positive and negative valence systems in major depression have distinct clinical features, response to antidepressants, and relationships with immunomarkers. Depress Anxiety 2020;37(8):771–83. 10.1002/da.23006. [PubMed: 32187776]

[20]. Kessel EM, Kujawa A, Goldstein B, Hajcak G, Bufferd SJ, Dyson M, et al. Behavioral observations of positive and negative valence systems in early childhood predict physiological measures of emotional processing three years later. J Affect Disord 2017;216:70–7. 10.1016/j.jad.2016.10.044. [PubMed: 27829516]

[21]. Kujawa A, Klein DN, Pegg S, Weinberg A. Developmental trajectories to reduced activation of positive valence systems: a review of biological and environmental contributions. Dev Cogn Neurosci 2020;43:100791. 10.1016/j.dcn.2020.100791. [PubMed: 32510349]

[22]. Kujawa A, Carroll A, Mumper E, Mukherjee D, Kessel EM, Olino T, et al. A longitudinal examination of event-related potentials sensitive to monetary reward and loss feedback from late childhood to middle adolescence. Int J Psychophysiol 2018;132:323–30. 10.1016/j.ijpsycho.2017.11.001. [PubMed: 29113953]

[23]. Pegg S, Dickey L, Mumper E, Kessel E, Klein DN, Kujawa A. Stability and change in emotional processing across development: a 6-year longitudinal investigation using event-related potentials. Psychophysiology 2019. 10.1111/psyp.13438.

[24]. Kujawa A, Proudfit GH, Kessel EM, Dyson M, Olino T, Klein DN. Neural reactivity to monetary rewards and losses in childhood: Longitudinal and concurrent associations

with observed and self-reported positive emotionality. Biol Psychol 2015;104:41–7. 10.1016/j.biopsycho.2014.11.008. [PubMed: 25433097]

[25]. Proudfit GH. The reward positivity: from basic research on reward to a biomarker for depression. Psychophysiology 2015;52(4):449–59. 10.1111/psyp.12370. [PubMed: 25327938]

[26]. Becker MPI, Nitsch AM, Miltner WHR, Straube T. A single-trial estimation of the feedback-related negativity and its relation to BOLD responses in a time-estimation task. J Neurosci 2014;34(8):3005–12. 10.1523/JNEUROSCI.3684-13.2014. [PubMed: 24553940]

[27]. Carlson JM, Foti D, Mujica-Parodi LR, Harmon-Jones E, Hajcak G. Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: a combined ERP and fMRI study. Neuroimage 2011;57(4): 1608–16. 10.1016/j.neuroimage.2011.05.037. [PubMed: 21624476]

[28]. Foti D, Carlson JM, Sauder CL, Proudfit GH. Reward dysfunction in major depression: multimodal neuroimaging evidence for refining the melancholic phenotype. NeuroImage 2014;101:50–8. 10.1016/j.neuroimage.2014.06.058. [PubMed: 24996119]

[29]. Weinberg A, Hajcak G. Beyond good and evil: the time-course of neural activity elicited by specific picture content. Emotion 2010;10(6):767–82. 10.1037/a0020242. [PubMed: 21058848]

[30]. Bunford N, Kujawa A, Fitzgerald KD, Monk CS, Phan KL. Convergence of BOLD and ERP measures of neural reactivity to emotional faces in children and adolescents with and without anxiety disorders. Biol Psychol 2018;134. 10.1016/j.biopsycho.2018.02.006.

[31]. Liu Y, Huang H, McGinnis-Deweese M, Keil A, Ding M. Neural substrate of the late positive potential in emotional processing. J Neurosci 2012;32(42):14563–72. 10.1523/JNEUROSCI.3109-12.2012. [PubMed: 23077042]

[32]. Bress JN, Foti D, Kotov R, Klein DN, Hajcak G. Blunted neural response to rewards prospectively predicts depression in adolescent girls. Psychophysiology 2013;50 (1):74–81. 10.1111/j.1469-8986.2012.01485.x. [PubMed: 23252717]

[33]. Bress JN, Meyer A, Proudfit GH. The stability of the feedback negativity and its relationship with depression during childhood and adolescence. Dev Psychopathol 2015;17:1285–94. 10.1017/S0954579414001400.

[34]. Dickey L, West M, Pegg S, Green H, Kujawa A. Neurophysiological responses to interpersonal emotional images prospectively predict the impact of COVID-19 pandemic–related stress on internalizing symptoms. Biol Psychiatry: Cogn Neurosci Neuroimag. 2021. 10.1016/j.bpsc.2021.03.004.

[35]. Kujawa A, Hajcak G, Klein DN. Reduced reward responsiveness moderates the effect of maternal depression on depressive symptoms in offspring: evidence across levels of analysis. J Child Psychol Psychiatry 2019;60(1):82–90. 10.1111/jcpp.12944. [PubMed: 29978904]

[36]. Nelson BD, Perlman G, Klein DN, Kotov R, Hajcak G. Blunted neural response to rewards prospectively predicts the development of depression in adolescent girls. Am J Psychiatry 2016;173(12):1223–30. 10.1176/appi.ajp.2016.15121524. [PubMed: 27363510]

[37]. Proudfit GH, Bress JN, Foti D, Kujawa A, Klein DN. Depression and event-related potentials: Emotional disengagement and reward insensitivity. Curr Opin Psychol 2015;4:110–3. 10.1007/128. [PubMed: 26462292]

[38]. Foti D, Olvet DM, Klein DN, Hajcak G. Reduced electrocortical response to threatening faces in major depressive disorder. Depress Anxiety 2010;27(9): 813–20. 10.1002/da.20712. [PubMed: 20577985]

[39]. Hill KE, South SC, Egan RP, Foti D. Abnormal emotional reactivity in depression: contrasting theoretical models using neurophysiological data. Biol Psychol 2019; 141. 10.1016/j.biopsycho.2018.12.011.

[40]. Michelini G, Perlman G, Tian Y, Mackin DM, Nelson BD, Klein DN, et al. Multiple domains of risk factors for first onset of depression in adolescent girls. J Affect Disord 2021;283:20–9. 10.1016/j.jad.2021.01.036. [PubMed: 33516083]

[41]. Weinberg A, Perlman G, Kotov R, Hajcak G. Depression and reduced neural response to emotional images: distinction from anxiety, and importance of symptom dimensions and age of onset. J Abnorm Psychol 2016;125(1):26–39. 10.1037/abn0000118. [PubMed: 26726817]

[42]. Auerbach RP, Stanton CH, Proudfit GH, Pizzagalli DA. Self-referential processing in depressed adolescents: a high-density event-related potential study. J Abnorm Psychol 2015;124(2):233–45. 10.1037/abn0000023. [PubMed: 25643205]

[43]. Speed BC, Nelson BD, Auerbach RP, Klein DN, Hajcak G. Depression risk and electrocortical reactivity during self-referential emotional processing in 8 to 14-year-old girls. J Abnorm Psychol 2016. 10.1037/abn0000173.

[44]. Benau EM, Hill KE, Atchley RA, O'Hare AJ, Gibson LJ, Hajcak G, et al. Increased neural sensitivity to self-relevant stimuli in major depressive disorder. Psychophysiology 2019;56(7). 10.1111/psyp.13345.

[45]. Klawohn J, Burani K, Bruchnak A, Santopetro N, Hajcak G. Reduced neural response to reward and pleasant pictures independently relate to depression. Psychol Med 2021;51(5):741–9. [PubMed: 31907094]

[46]. Kupferberg A, Bicks L, Hasler G. Social functioning in major depressive disorder. Neurosci Biobehav Rev 2016;69:313–32. 10.1016/j.neubiorev.2016.07.002. [PubMed: 27395342]

[47]. Goldstein BL, Kessel EM, Kujawa A, Finsaas MCMC, Davila J, Hajcak G, et al. Stressful life events moderate the effect of neural reward responsiveness in childhood on depressive symptoms in adolescence. Psychol Med 2019;50(9). 10.1017/S0033291719001557.

[48]. Pegg S, Ethridge P, Shields GSS, Slavich GMM, Weinberg A, Kujawa A. Blunted social reward responsiveness moderates the effect of lifetime social stress exposure on depressive symptoms. Front Behav Neurosci 2019;13. 10.3389/fnbeh.2019.00178.

[49]. Shih JH, Eberhart NK, Hammen CL, Brennan PA. Differential exposure and reactivity to interpersonal stress predict sex differences in adolescent depression. J Clin Child Adolesc Psychol 2006;35(1):103–15. 10.1207/s15374424jccp3501_9. [PubMed: 16390306]

[50]. Vrshek-Schallhorn S, Stroud CB, Mineka S, Hammen C, Zinbarg RE, Wolitzky-Taylor K, et al. Chronic and episodic interpersonal stress as statistically unique predictors of depression in two samples of emerging adults. J Abnorm Psychol 2015;124(4):918–32. 10.1037/abn0000088. [PubMed: 26301973]

[51]. Crone EA, Dahl RE. Understanding adolescence as a period of social-affective engagement and goal flexibility. Nat Rev Neurosci 2012;13(9):636–50. 10.1038/nrn3313. [PubMed: 22903221]

[52]. Davey CG, Yucel M, Allen NB. The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. Neurosci Biobehav Rev 2008;32:1–19. 10.1016/j.neubiorev.2007.04.016. [PubMed: 17570526]

[53]. Smetana JG, Campione-Barr N, Metzger A. Adolescent development in interpersonal and societal contexts. Annu Rev Psychol 2006;57:255–84. 10.1146/annurev.psych.57.102904.190124. [PubMed: 16318596]

[54]. Dickey L, Pegg S, Kujawa A. Neurophysiological responses to interpersonal emotional images: associations with symptoms of depression and social anxiety. Cogn, Affect, Behav Neurosci 2021;21:1306–18. 10.3758/s13415-021-00925-6. [PubMed: 34272679]

[55]. Ethridge P, Kujawa A, Dirks MA, Arfer KB, Kessel AM, Klein DN, et al. Neural responses to social and monetary reward in early adolescence and emerging adulthood. Psychophysiology 2017;(12):1786–99. 10.1111/psyp.12957. [PubMed: 28700084]

[56]. Kujawa A, Kessel EM, Carroll A, Arfer KB, Klein DN. Social processing in early adolescence: associations between neurophysiological, self-report, and behavioral measures. Biol Psychol 2017;128:55–62. 10.1016/j.biopsycho.2017.07.001. [PubMed: 28712730]

[57]. Pegg S, Arfer KB, Kujawa A. Altered reward responsiveness and depressive symptoms: an examination of social and monetary reward domains and interactions with rejection sensitivity. J Affect Disord 2021;282:717–25. 10.1016/j.jad.2020.12.093. [PubMed: 33601712]

[58]. Pegg S, Dickey L, Green H, Kujawa A. Differentiating clinically depressed adolescents with and without active suicidality: an examination of neurophysiological and self-report measures of reward responsiveness. Depress Anxiety 2020;37(9):876–84. 10.1002/da.23012. [PubMed: 32248653]

[59]. Pegg S, Lytle MN, Arfer KB, Kujawa A. The time course of reactivity to social acceptance and rejection feedback: An examination of event-related potentials and behavioral measures in a peer interaction task. Psychophysiology 2022:e14007. 10.1111/psyp.14007. [PubMed: 35193158]

[60]. Kujawa A, Arfer KB, Klein DN, Proudfit GH. Electrocortical reactivity to social feedback in youth: a pilot study of the Island Getaway task. Dev Cogn Neurosci 2014;10:140–7. 10.1016/j.dcn.2014.08.008. [PubMed: 25212683]

[61]. Patrick CJ, Venables NC, Yancey JR, Hicks BM, Nelson LD, Kramer MD. A construct-network approach to bridging diagnostic and physiological domains: application to assessment of externalizing psychopathology. J Abnorm Psychol 2013;122(3):902. 10.1037/a0032807. [PubMed: 24016026]

[62]. Peng Y, Knotts JD, Taylor CT, Craske MG, Stein MB, Bookheimer S, et al. Failure to identify robust latent variables of positive or negative valence processing across units of analysis. Biol Psychiatry: Cogn Neurosci Neuroimaging 2021;6(5):518–26. 10.1016/j.bpsc.2020.12.005. [PubMed: 33676919]

[63]. Goodman SH, & Tully E (2008). Children of depressed mothers. In Abela JRZ & Hankin BL (Eds.), Handbook of depression in children and adolescents (pp. 415–440). Guilford Press.

[64]. First MB, Williams JB, Karg RS, & Spitzer RL (2016). Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV). American Psychiatric Association.

[65]. Kaufman J, Birmaher B, Axelson D, Perepletchikova F, Brent D, & Ryan N (2016). The Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version for DSM-5.

[66]. Angold A, Costello EJ, Messer SC, Pickles A, Winder F, Silver D. Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. Int J Methods Psychiatr Res 1995;5:237–49.

[67]. Kujawa A, Klein DN, Proudfit GHGH. Two-year stability of the late positive potential across middle childhood and adolescence. Biol Psychol 2013;94(2): 290–6. 10.1002/dev.21058. [PubMed: 23872165]

[68]. Simmons AM, Luck SJ. Protoc Reducing COVID-19 Transm Risk EEG Res Res Sq 2020. 10.21203/rs.3.pex-974/v2.

[69]. Hajcak G, Weinberg A, MacNamara A, & Foti D (2012). ERPs and the study of emotion. In Luck SJ & Kappenman ES (Eds.), The Oxford handbook of event-related potential components (pp. 441–472). Oxford University Press.

[70]. Gratton G, Coles MGH, Donchin E. A new method for off-line removal of ocular artifact. Electroencephalogr Clin Neurophysiol 1983;55(4):468–84. [PubMed: 6187540]

[71]. Rappaport BIBI, Hennefield L, Kujawa A, Arfer KBKB, Kelly D, Kappenman ESES, et al. Peer victimization and dysfunctional reward processing: ERP and behavioral responses to social and monetary rewards. Front Behav Neurosci 2019;13:120. 10.3389/fnbeh.2019.00120. [PubMed: 31213997]

[72]. Meyer A, Lerner MD, De Los Reyes A, Laird RD, Hajcak G. Considering ERP difference scores as individual difference measures: Issues with subtraction and alternative approaches. Psychophysiology 2017;54(1):114–22. 10.1111/psyp.12664. [PubMed: 28000251]

[73]. Wickham H, Averick M, Bryan J, Chang W, McGowan LD, François R, et al. Welcome to the tidyverse. J Open Source Softw 2019;4(43):1686. 10.21105/joss.01686.

[74]. Wickham H, Francois R, Henry L, & Müller K (2014). dplyr. UseR! Conference.

[75]. Maechler M, Rousseeuw P, Struyf A, Hubert M, Hornik K, & Studer M (2013). Package 'cluster.' Dosegljivo Na.

[76]. Auguie B (2017). _gridExtra: Miscellaneous Functions for "Grid" Graphics_. R package version 2.3, https://CRAN.R-project.org/package=gridExtra.

[77]. Kassambara A, Mundt F. Package 'factoextra. Extr Vis Results Multivar Data Anal 2017;76(2).

[78]. Syakur MA, Khotimah BK, Rochman EMS, Satoto BD. Integration k-means clustering method and elbow method for identification of the best customer profile cluster. IOP Conf Ser: Mater Sci Eng 2018;336(1):012017. 10.1088/1757-899X/336/1/012017.

[79]. Rousseeuw PJ. Silhouettes: a graphical aid to the interpretation and validation of cluster analysis. J Comput Appl Math 1987;20:53–65.

[80]. Ait Oumeziane B, Foti D. Reward-related neural dysfunction across depression and impulsivity: a dimensional approach. Psychophysiology 2016;53(8):1174–84. 10.1111/psyp.12672. [PubMed: 27193188]

[81]. Burani K, Klawohn J, Levinson AR, Klein DN, Nelson BD, Hajcak G. Neural response to rewards, stress and sleep interact to prospectively predict depressive symptoms in adolescent girls. J Clin Child Adolesc Psychol 2021;50(1):131–40. 10.1080/15374416.2019.1630834. [PubMed: 31328972]

[82]. Hager NM, Judah MR, Rawls E. Win, lose, or draw: examining salience, reward memory, and depression with the reward positivity. Psychophysiology 2022;59(1). 10.1111/psyp.13953.

[83]. Hill KE, Dickey L, Pegg S, Dao A, Arfer KB, Kujawa A. Associations between parental conflict and social and monetary reward responsiveness in adolescents with clinical depression. Res Child Adolesc Psychopathol 2023;51(1):119–31. 10.1007/s10802-022-00949-7. [PubMed: 35852700]

[84]. Nelson BD, Infantolino ZP, Klein DN, Perlman G, Kotov R, Hajcak G. Time-frequency reward-related delta prospectively predicts the development of adolescent-onset depression. Biol Psychiatry: Cogn Neurosci Neuroimaging 2018;3 (1):41–9. 10.1016/j.bpsc.2017.07.005. [PubMed: 29397078]

[85]. Webb CA, Auerbach RP, Bondy E, Stanton CH, Appleman L, Pizzagalli DA. Reward-related neural predictors and mechanisms of symptom change in cognitive behavioral therapy for depressed adolescent girls. Biol Psychiatry: Cogn Neurosci Neuroimaging 2021;6(1):39–49. 10.1016/j.bpsc.2020.07.010. [PubMed: 32948509]

[86]. Silk JS, Forbes EE, Whalen DJ, Jakubcak JL, Thompson WK, Ryan ND, et al. Daily emotional dynamics in depressed youth: A cell phone ecological momentary assessment study. J Exp Child Psychol 2011;110(2):241–57. 10.1016/j.jecp.2010.10.007. [PubMed: 21112595]

[87]. Burkhouse KL, Kujawa A, Kennedy AE, Shankman SA, Langenecker SA, Phan KL, et al. Neural reactivity to reward as a predictor of cognitive behavioral therapy response in anxiety and depression. Depress Anxiety 2016;33(4):281–8. 10.1002/da.22482. [PubMed: 27038409]

[88]. Kujawa A, Burkhouse KL, Karich SR, Fitzgerald KD, Monk CS, Phan KL. Reduced reward responsiveness predicts change in depressive symptoms in anxious children and adolescents following treatment. J Child Adolesc Psychopharmacol 2019;29 (5):378–85. 10.1089/cap.2018.0172. [PubMed: 31062997]

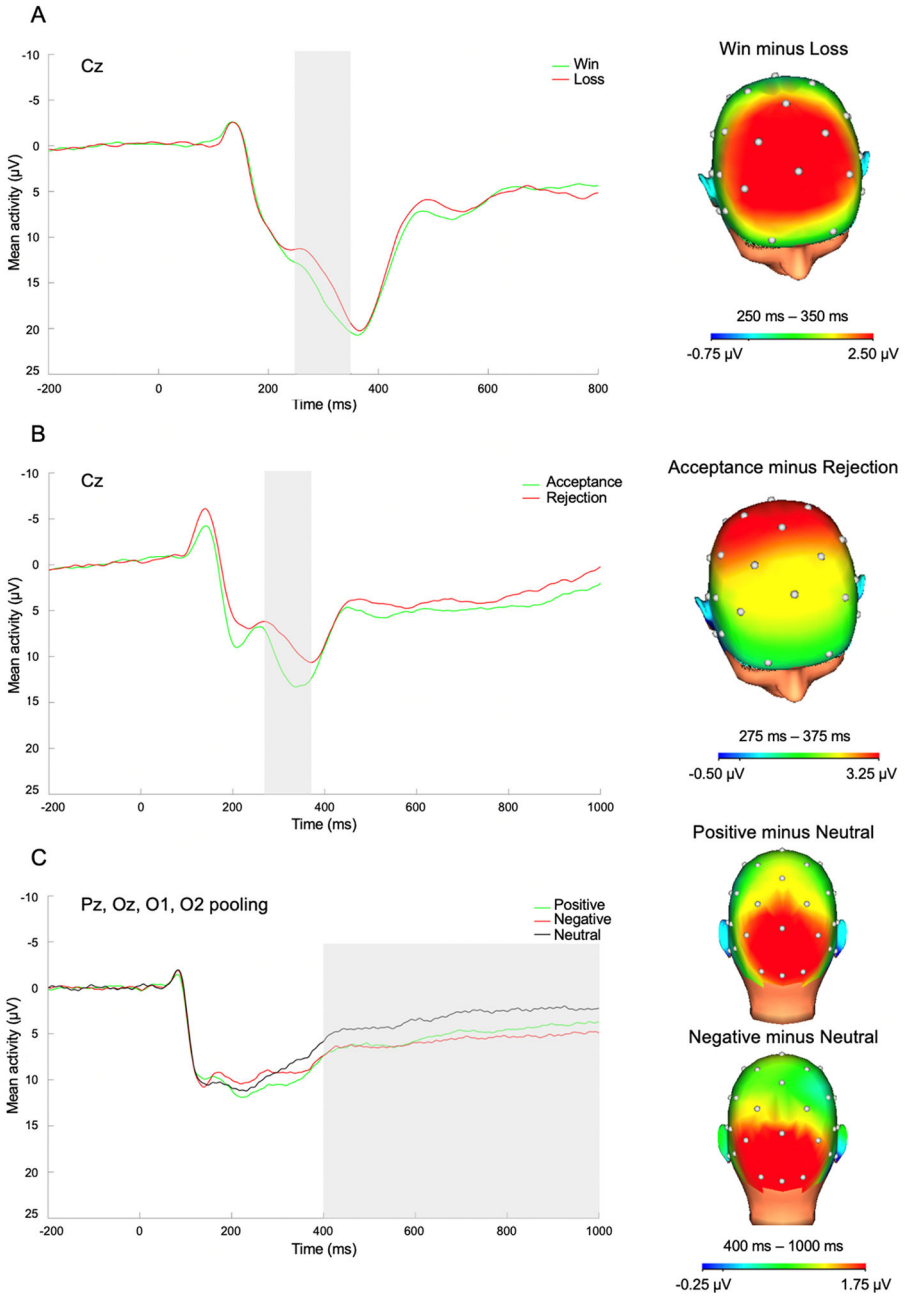

Fig. 1.

ERP waves and scalp topographies depicting neural responses for (A) monetary RewP, (B) social RewP, and (C) positive and negative LPP in the full sample.

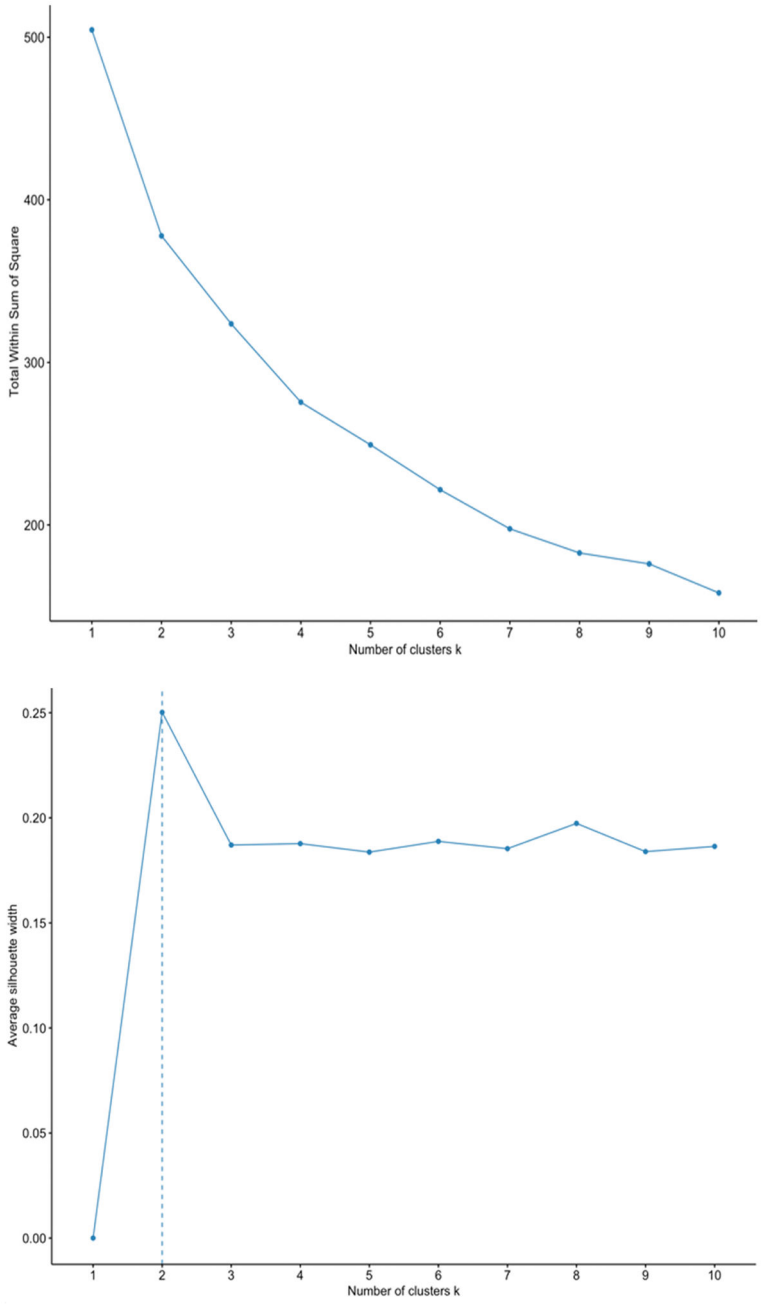

Fig. 2.

Elbow (top) and silhouette (bottom) plots illustrating $k = 2$ as the optimal number of clusters characterizing the patterns of PVS and NVS function across neural measures. The elbow plot illustrates decreased slope in the total within sum of squares after the two-cluster solution. The silhouette plot indicates that two clusters have the largest average silhouette width, a measure of how similar an object is to its own cluster (i.e., minimal within-group variability) compared to other clusters (i.e., maximal between-group variability).

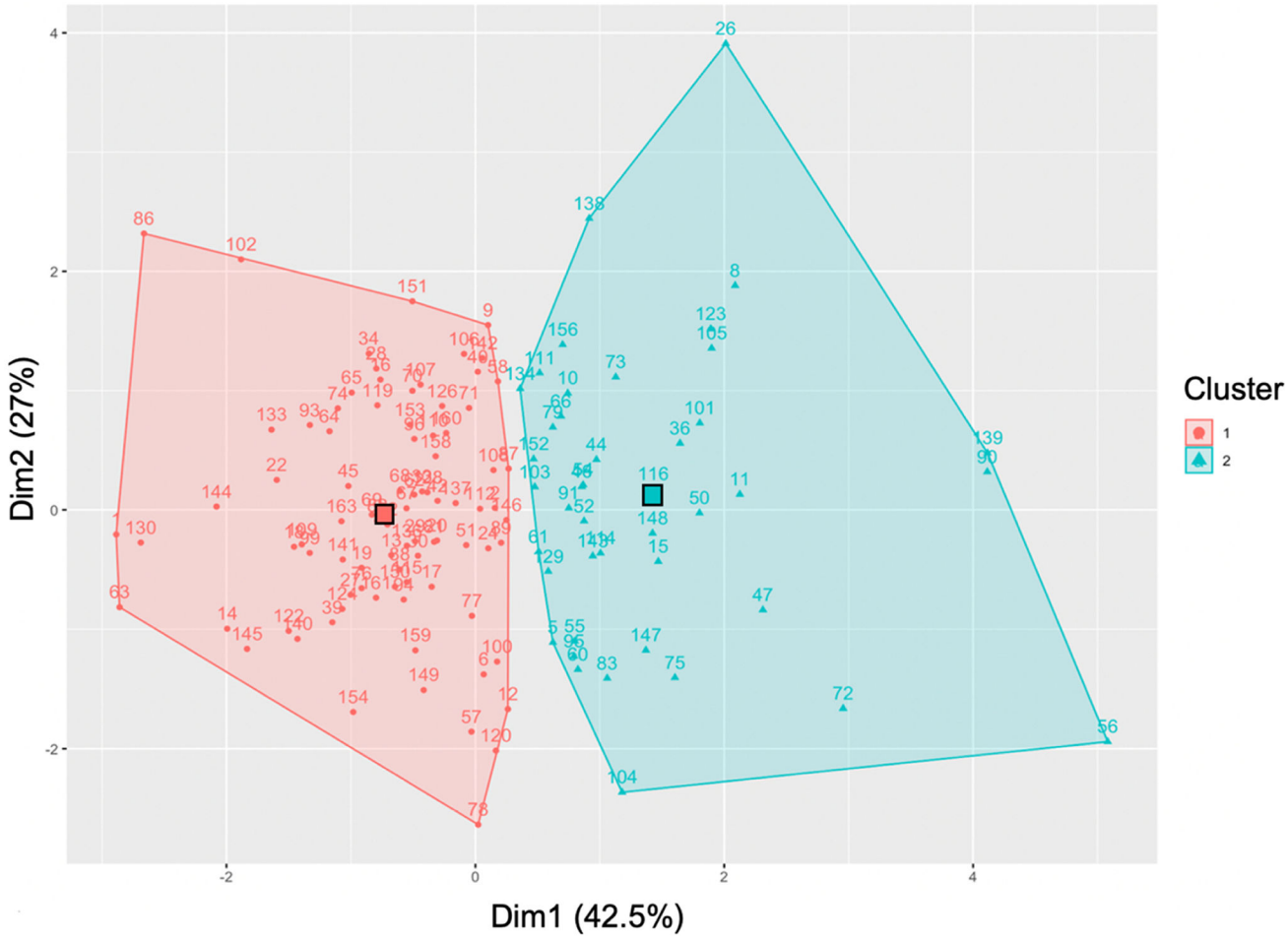

Fig. 3.

Top: Cluster plot with $k = 2$. Cluster 1 is presented in red, with each circle comprising one observation. Cluster 2 is presented in blue, with each triangle comprising one observation. Respective squares outlined in black represent the cluster centers. Axes reflect a principal component analysis on the 4 neural measures used in the cluster analysis for illustrative utility. Observed values are plotted according to the first two principal components derived that explain a majority of the variance for cluster visualization purposes, labeled as dimensions (Dim1 and Dim2, respectively) according to the amount of variance accounted for indicated in parentheses. As demonstrated, the two-cluster solution did not contain any observation overlap between clusters. Bottom: Bar chart reflecting mean ERP values in standardized units.

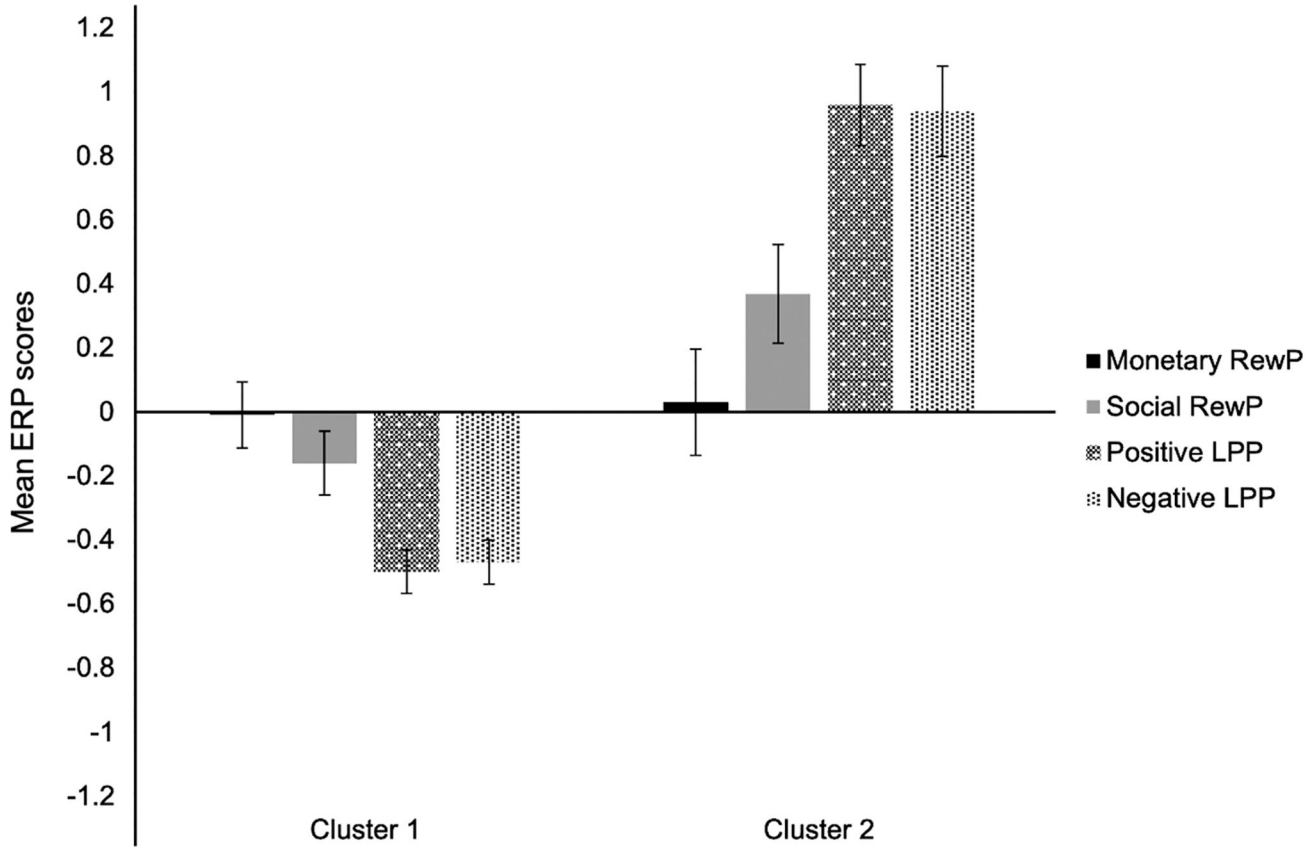

Fig. 4.

Means and standard errors for standardized ERP residual scores by cluster. Cluster 1 was characterized by blunted responsiveness across components, and cluster 2 was characterized by relatively intact responsiveness.

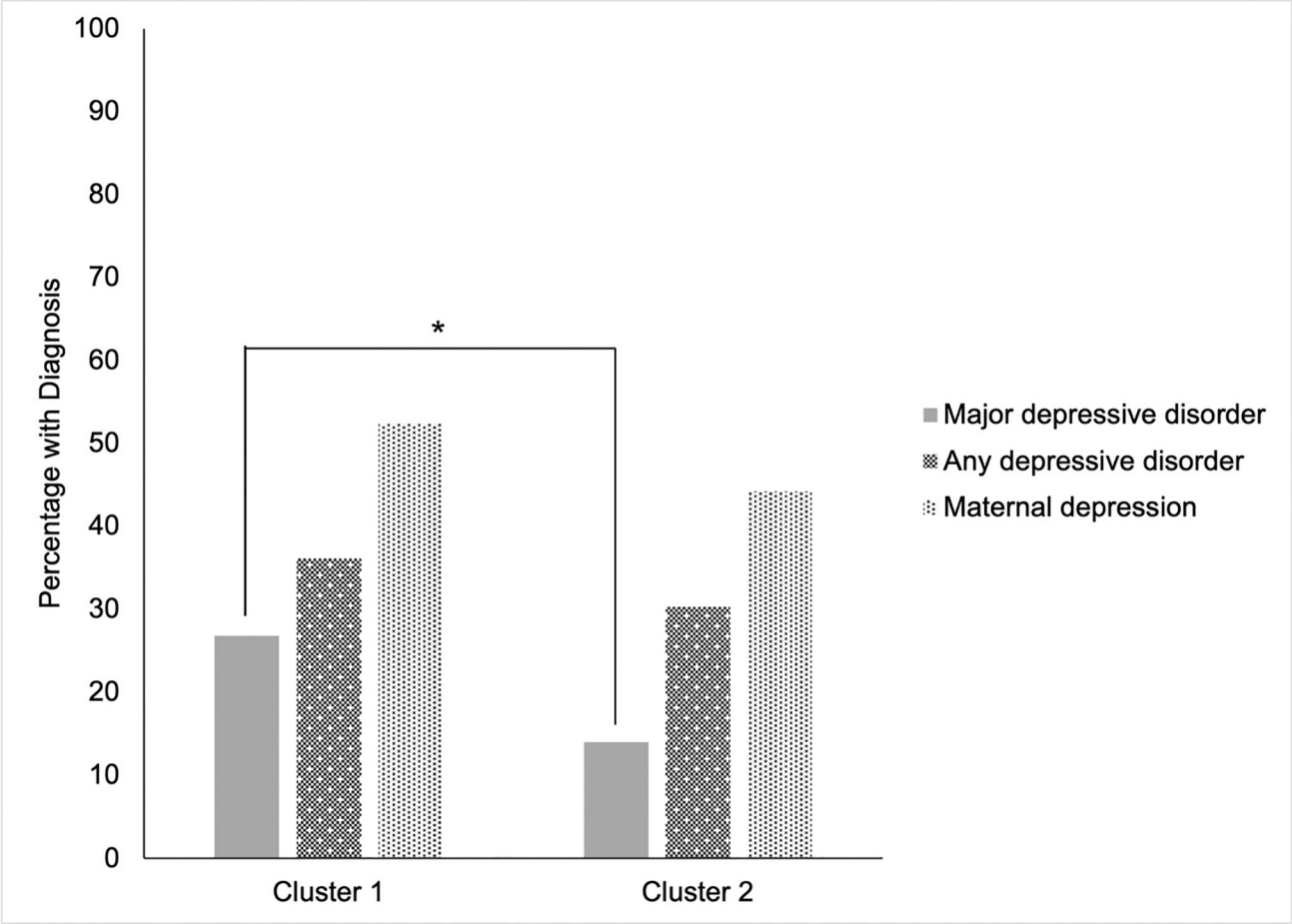

Fig. 5.

Percentage of participants with any depressive disorder diagnosis, major depressive disorder diagnosis, and maternal history of depression diagnosis by cluster. Cluster 1 was characterized by blunted responsiveness across components, and cluster 2 was characterized by relatively intact responsiveness.

Table 1

Bivariate associations of each ERP and cluster membership with indicators of depression and depression risk.

	1	2	3	4	5	6	7	8
1. Monetary RewP	-							
2. Social RewP	.09 [− .06,.23]	-						
3. Positive LPP	−.05 [− .20,.09]	.12 [− .02,.26]	-					
4. Negative LPP	−.05 [− .19,.10]	.15 *[.00,.29]	.65 **[.55,.72]	-				
5. Cluster membership	.02 [− .13,.16]	.26 **[.11,.39]	.70 **[.62,.77]	.67 **[.58,.74]	-			
6. Depressive disorder	.09 [− .06,.23]	−.08 [− .23,.06]	−.03 [− .18,.12]	−.04 [− .18,.11]	−.06 [− .20,.09]	-		
7. MDD	.04 [− .12,.19]	−.11 [− .26,.05]	−.15 *[− .30,.00]	−.14 [− .29,.01]	−.18 *[− .32, − .02]	.77 **[.70,.82]	-	
8. Maternal depressive disorder	−.02 [− .17,.13]	−.04 [− .19,.10]	.03 [− .12,.18]	−.08 [− .22,.07]	−.06 [− .20,.09]	.33 **[.19,.45]	.30 **[.15,.43]	-
9. Self-reported depressive symptoms	−.01 [− .16,.13]	−.14 [− .28,.01]	−.07 [− .22,.08]	−.11 [− .26,.04]	−.15 *[− .29, − .01]	.64 **[.54,.72]	.60 **[.50,.70]	.22 **[.08,.36]

Note.

*$p < .05$,

**$p < .01$.

All p values reflect one-tailed significance testing. Pearson's r used to examine associations amongst continuous and dichotomous variables. Kendall's τ_b was used to examine associations between two dichotomous variables. 90% CI indicated in []. Diagnoses were collected from clinical interviews (KSADS and SCID); Self-reported depressive symptoms = MFQ.