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Neurocognitive Risk Phenotyping to Predict Mood Symptoms in Adolescence

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Abstract

Predicting mood disorders in adolescence is a challenge that motivates research to identify neurocognitive predictors of symptom expression and clinical profiles. This study used machine learning to test whether neurocognitive variables predicted future manic or anhedonic symptoms in two adolescent samples risk-enriched for lifetime mood disorders (Sample 1, *n*=73, ages 13–25, M (SD)=19.22 (2.49) years, 68% lifetime mood disorder) or familial mood disorders (Sample

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Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship or the publication of this article.

Prior Dissemination of the Data and Ideas

Sample 1 overlaps with a sample of adolescents in which other, non-overlapping behavioral hypotheses were tested (Peterson et al., 2021, 2022). Participants in Sample 2 are part of an ongoing multi-year study (the current study focuses on the first wave of assessment, and other procedures and timepoints will be reported elsewhere). Subsets of Samples 1 and 2 were included in a pooled behavioral analysis reported elsewhere (Kaiser et al., 2022). This study is the first to investigate neurocognitive prediction, or to report on neuroimaging data, in either sample.

Research Ethics Committee Approval

Research protocols were approved by the Institutional Review Boards at the University of Colorado Boulder and the University of California Los Angeles (UCLA 16–001894, CUB 18–0600, CUB 18–0415).

2, *n*=154, ages 13–21, M (SD)=16.46 (1.95) years, 62% first-degree family history of mood disorder). Participants completed cognitive testing and functional magnetic resonance imaging at baseline, for behavioral and neural measures of reward processing and executive functioning. Next, participants completed a daily diary procedure for eight to sixteen weeks. Penalized mixed effects models identified neurocognitive predictors of future mood symptoms and stress-reactive changes in mood symptoms. Results included the following. In both samples, adolescents showing ventral corticostriatal reward hyposensitivity and lower reward performance reported more severe stress-reactive anhedonia. Poorer executive functioning behavior was associated with heightened anhedonia overall in Sample 1, but lower stress-reactive anhedonia in both samples. In Sample 1, adolescents showing ventral corticostriatal reward hypersensitivity and poorer executive functioning reported more severe stress-reactive manic symptoms. Clustering analyses identified, and replicated, five neurocognitive subgroups. Adolescents characterized by neural or behavioral reward hyposensitivities together with average-to-poor executive functioning reported unipolar symptom profiles. Adolescents showing neural reward hypersensitivity together with poor behavioral executive functioning reported a bipolar symptom profile (Sample 1 only). Together, neurocognitive phenotypes may hold value for predicting symptom expression and profiles of mood pathology.

General Scientific Summary:

Discovery of reliable cognitive and brain markers of risk may help to predict mood problems in adolescence. This study identified neurocognitive risk markers in two independent groups of adolescents, showing that combined abnormalities in brain and behavioral reward responses, and in executive functioning abilities, characterized subgroups who reported distinctive profiles of mood symptoms over the next two to four months.

Keywords

reward; executive functioning; functional network; mania; anhedonia; adolescent

Mood disorders, including unipolar and bipolar disorders, often emerge during adolescence (Paus et al., 2008), a developmental period that has been defined as beginning with puberty and ending with the transition to independence in social-emotional functioning (Forbes & Dahl, 2010). Yet, distinguishing the boundaries between mood disorders and identifying predictors of future outcomes remain clinical challenges (Cuthbert & Insel, 2010). Cardinal symptom dimensions such as anhedonia characterize patients with either bipolar and unipolar disorders (Hoertel et al., 2016), whereas mania and hypomania, while mainly characterizing bipolar patients, are present at subthreshold levels of severity in 25%-40% of unipolar patients (Zimmermann et al., 2009). Clinical heterogeneity is further complicated by the dynamic nature of mood disorders: patients experience fluctuations in several symptom dimensions on variable timescales (e.g., days, weeks) and in response to life stress (Peterson et al., 2021). Clinical heterogeneity is especially marked among adolescent patients (Birmaher & Axelson, 2006), rendering differential diagnosis more difficult in a population in which early intervention is critically important.

In the face of these challenges, clinical science has turned to new strategies for predicting mood pathology, with special interest in neurocognitive markers that may be proximal to mechanisms of pathophysiology. Prior research has demonstrated neurocognitive abnormalities in mood disorders, including in dimensions of *executive functioning*, defined as higher-order cognitive abilities and related neural systems that support goal-directed behavior and adaptation (Friedman et al., 2018); and dimensions of *reward sensitivity*, defined as an individual's behavioral, physiological, or emotional responsiveness to rewards (Berridge, 2018). Executive functioning ability and reward sensitivity are neurocognitive domains that show marked developmental change during adolescence and young adulthood, suggesting the importance of understanding how adolescent abnormalities in these domains may forecast risk both in the near future and across the lifespan (Kaiser et al., 2022).

Adolescents with unipolar and bipolar disorders exhibit deficits in executive functioning (Horn et al., 2011; Wagner et al., 2015). Such deficits have been observed at comparable effect sizes across subdimensions of executive functioning, suggesting mood-related impairment in "common" executive functioning that broadly disrupts goal-directed behavior (Snyder, 2013). In turn, common executive dysfunction is observed across mood disorders (Snyder et al., 2019), putatively driving shared psychopathological processes that correspond with distress, overlapping symptoms, or symptom severity (Peterson et al., 2022). Critically, poor executive functioning may be a risk marker for future mood pathology. For example, adolescents who exhibited lower lateral frontoinsular functional connectivity in response to a working memory task reported more severe and labile negative affect in daily life and increases in depression in the next several weeks (Kaiser et al., 2019). However, other studies have reported equivocal evidence for executive dysfunction as a risk marker (Scult et al., 2017). Given the clinical heterogeneity of mood disorders, one possibility is that executive dysfunction characterizes subgroups at risk for more severe and recurrent symptoms (Van Rheenen et al., 2020). Together, while there is support for executive dysfunction across adolescent mood disorders, it remains unclear the extent to which such dysfunction characterizes subgroups or predicts future symptoms.

In contrast to common patterns of executive dysfunction, abnormalities in reward processing are differentially associated with unipolar versus bipolar symptom profiles. Unipolar depression has been consistently associated with reward hyposensitivity (Ng et al., 2019), including reduced behavioral approach of and corticostriatal response to reward (Pizzagalli, 2014). In turn, complex abnormal reward sensitivities have been observed in individuals with bipolar disorders including increased activity in ventral striatal and orbitofrontal regions in response to reward, (Alloy & Nusslock, 2019), but also blunted behavioral biases towards reward (Pizzagalli et al., 2008). As with executive dysfunction, prior work also indicates that abnormal reward sensitivity prospectively predicts mood pathology. For example, increased self-reported or corticostriatal response to reward predicted onset of a manic episode (Nusslock & Alloy, 2017) and blunted corticostriatal response to reward predicted worsening depression (Nielson et al., 2021). However, there are mixed findings for the reliability with which reward anomalies predict future symptoms, and effect sizes are small and vary with age (Nielson et al., 2021). Such mixed findings may be attributable in part to unmeasured contextual factors that interact with neurocognitive functioning to instantiate risk. In particular, life stress is associated with increased severity of mood

symptoms (Monroe & Reid, 2009), and neurocognitive risk may be a catalyst for stress to exacerbate mood pathology (Pizzagalli, 2014). However, the prospective associations between neurocognitive vulnerabilities and stress-related fluctuations in mood symptoms are not well understood.

In sum, prior research provides evidence that executive dysfunction and abnormal reward responses predict mood pathology in adolescence. However, there are several gaps. First, neurocognitive variables should be linked to the real-world expression of symptoms over time, in daily life and in response to stress. Such investigation should be performed in samples who vary in known risk factors for mood disorders, to maximize variance in symptom expression over time and better characterize neurocognitive risk. Second, neurocognitive risk should be characterized using multiple measures and robust predictive approaches. Neural and behavioral indices hold complementary information about neurocognitive functioning, hence multimodality may improve risk prediction when combined with analytic approaches that select robust predictors. Third, it is valuable to explore profiles of combined neurocognitive features that characterize subgroups of adolescents. Data-driven approaches to identify neurocognitive phenotypes on the basis of combined features can provide insight into the real-world manifestation of neurocognitive risk (Drysdale et al., 2017; Miranda et al., 2021). In the present study, we addressed these gaps.

This study collected behavioral and neural measures of reward processing and executive functioning in two risk-enriched adolescent samples, and used machine learning approaches to identify neurocognitive variables that predicted stress-related changes in symptoms of mania or anhedonic depression over a period of eight (Sample 1) to sixteen (Sample 2) weeks. The first sample was risk-enriched on the basis of personal history of mood disorders (n=73, ages 13 to 25 years, 68% lifetime mood disorder). The second sample was risk-enriched on the basis of familial history of mood disorders (n=154, ages 13 to 21 years, 62% with a first-degree relative with a diagnosed mood disorder). In this study, adolescence was operationalized as the period spanning puberty onset through the social-emotional transition to independence (Forbes & Dahl, 2010). We note that other developmental theories may characterize our samples as including both adolescence and emerging adulthood (Arnett, 2000). Our approach was aimed at capturing a full window of high risk for mood symptom onset, consistent with age ranges in prior risk prediction research (e.g., reviews in Faedda et al., 2014; Pedersen et al., 2023). (However, see Discussion for limitations of this approach).

Behaviorally, neurocognitive functioning was measured with a multi-task design that yielded behavioral factors for reward performance and common executive functioning. Neural measures of reward sensitivity included functional connectivity in response to reward in a ventral corticostriatal network involved in reward valuation and responding to reward outcomes, and a dorsal corticostriatal network involved in agentic reward-seeking and effort (Rushworth et al., 2011). Neural measurement of executive functioning included functional connectivity in response to task demands for cognitive control in frontoinsular networks including insula and either lateral (Sridharan et al., 2008), or anterior prefrontal regions (Vincent et al., 2008). Daily stress, and anhedonic and manic/hypomanic symptom severity, were evaluated with a daily diary.

Models were tested in Sample 1, then replicated in Sample 2. Penalized mixed-effects models identified neurocognitive variables that robustly predicted stress-reactive increases in anhedonic or manic symptoms (Greenwood et al., 2020). Clustering analyses identified neurocognitive phenotypes defined by combined neurocognitive features, and tested subgroup differences in symptoms and stress responses. Our hypotheses were that: (1) neurocognitive variables related to executive dysfunction and reward hyposensitivity would predict stress-reactive anhedonia; (2) neurocognitive variables related to executive dysfunction and reward hypersensitivity would predict stress-reactive manic symptoms; (3) distinct neurocognitive phenotypes would emerge from clustering analyses, and differentially predict unipolar or bipolar symptom trajectories over follow-up.

Method

Participants

Participants in Sample 1 were 73 individuals ages 13 to 25 years (M=19.22, SD=2.51) recruited to research at the University of Colorado Boulder and the University of California Los Angeles. Developmental inclusion criteria were anchored to age/pubertal status and social role: eligible participants were post-pubertal (based on the Pubertal Development Scale (Petersen et al., 1988)), between ages 13 and 25 years, and had not yet entered the workforce. In Sample 1, 46% of participants were in middle or high school, and 54% were in college (community college or four-year institution), at the time of study enrollment. Clinical inclusion criteria required a primary lifetime diagnosis of unipolar or bipolar mood disorders and currently elevated symptoms, or no lifetime diagnosis of psychopathology, to maximize variance in symptom expression (Tables 1, S1–S2).

Participants in Sample 2 were 154 individuals ages 13 to 21 years (M=16.46, SD=1.95) recruited to research at the University of Colorado Boulder. In Sample 2, 67% of participants were in middle or high school, and 33% were in college (community college or four-year institution), at the time of study enrollment. Clinical inclusion criteria required a first-degree relative with a primary lifetime diagnosis of unipolar or bipolar mood disorders, or no first-or-second-degree family members with diagnosed mood disorders (Tables 1, S1–S2).

Procedures

Participants in both samples completed a first in-person research session consisting of clinical evaluation, behavioral tests, and surveys, and a second in-person magnetic resonance imaging session no more than one week later.

Participants in both samples completed a daily diary consisting of the same items administered each day of the diary procedure, but with different schedules across samples. Sample 1 completed a daily diary consisting of a three-day series of daily surveys, administered once per week for eight weeks (24 timepoints). The first daily diary was anchored to the participant’s first research session, and the start day for each three-day series was lagged each week for better coverage of all weekdays over the assessment period. Participants in Sample 2 completed a daily diary consisting of a 21-day series of daily

surveys, administered once after baseline testing and repeated three months after baseline testing (42 timepoints).

The daily diary was sent as a unique link to an encrypted survey on the REDCap platform. Participants were instructed to complete their daily diary around the same time each day (within +/−2 hours); each daily link expired after 24 hours.

Research protocols were approved by the Institutional Review Boards at each site and were conducted in accordance with the provisions of the World Medical Association Declaration of Helsinki. Consent was obtained from adults (ages 18 and older) and parental consent and child assent was obtained from minors (ages 17 and younger).

Measures

Measures of neurocognitive functioning are briefly described below, with details in Supplement.

Behavioral Measures of Neurocognitive Functioning—Reward tasks included the Two-Armed Bandit Task, the Probabilistic Reward Task (Pizzagalli et al., 2005), and the Instrumental Learning Task (Collins & Frank, 2012). Reward tasks had overlapping instrumental learning demands and monetary rewards, but differed in their perceptual characteristics and task structure.

Executive functioning tasks included the Antisaccade Task, the Color-Shape Switching Task, and the Spatial N-Back Task (Friedman & Miyake, 2017; Friedman et al., 2016). Executive functioning tasks shared overlapping demands for goal-directed behavior, but differed in perceptual characteristics and recruitment of subdimensions of executive functioning.

Neuroimaging Measures of Neurocognitive Functioning—The Dice Guessing task was modeled after the Card Guessing task from the Human Connectome Project (Barch et al., 2013). This task evaluated neural response to anticipating and responding to monetary reward or monetary loss.

The N-Back task was the same task used in the Human Connectome Project (Barch et al., 2013). This task evaluated neural response to task demands for updating neutral visual stimuli held in working memory.

Daily Diary—The following were administered on every day of the daily diary, with instructions to respond based on the past 24 hours.

Daily stress.: Participants reported on the intensity of the most stressful event that happened on a scale of 1 = not stressful at all to 5 = extremely stressful. The single-item score indexed subjective stress intensity.

Mood and Anxiety Symptom Questionnaire- Loss of Interest (Anhedonia): (MASQ-LOI, (Watson, Clark, Weber, & Assenheimer, 1995). The MASQ-LOI evaluated severity of current anhedonic depression on a range of 1 (not at all) to 5 (extremely) for each item.

Per IRB recommendation, the item querying suicidality was omitted from the daily diary, yielding a 7-item scale. Items were summed for a total score.

General Behavior Inventory- Mania/Hypomania: (GBI-MH, (Depue et al., 1989)). The 10-item GBI-MH scale measured severity of current symptoms of mania or hypomania on a range of 0 (never or hardly ever) to 3 (very often or almost constantly) for each item. Items were summed for a total score.

Analyses

Behavioral Measures of Reward Performance—*Learning rate* was derived from a prediction error computational model applied to the Two-Armed Bandit Task (Frank et al., 2007), and is interpreted as the speed at which reward associations are learned. *Accuracy* was computed for the Instrumental Learning Task by estimating proportion accuracy over blocks, and reflects the ability to learn multiple stimulus-response associations. *Discriminability* was calculated for the Probabilistic Reward Task (Kaiser et al., 2018; Pizzagalli et al., 2005), and reflects the extent to which the participant is able to accurately discriminate between stimuli and reap maximum rewards. Of note, we also computed a second behavioral parameter (response bias) that has been more commonly associated with depression in prior research using this task. However, discriminability was selected for this study because it covaried with parameters from other reward tasks (whereas the response bias parameter did not). Therefore, discriminability was superior in terms of eligibility for factor analysis, see Supplement). Across reward processing tasks, the latent variable was the ability to learn and execute behaviors that maximize rewards.

Behavioral Measures of Executive Functioning—*Accuracy* on the Antisaccade Task provides a measure of the ability to inhibit prepotent behavioral responses (Friedman et al., 2016). *Accuracy* on the Spatial N-Back Task is a measure of working memory updating (Friedman et al., 2016). *Switch cost* on the Color-Shape Switching Task reflects response speed slowing when the participant must switch task conditions. Across executive functioning tasks, the latent variable was the ability to exert cognitive control and execute goal-directed behavior.

Confirmatory Factor Analyses for Behavioral Factors—Confirmatory factor analyses (CFAs) were performed in Mplus (Muthen & Muthen, 2017) using full information maximum likelihood estimation with robust standard error estimates to compute reward performance and executive functioning factors. The models were fitted on a pooled sample for better estimation and factor scores were saved using FSAVE.

Neuroimaging Measures of Neurocognitive Functioning—Neuroimaging processing and denoising are reported in Supplement. Task-modulated general linear models estimated functional connectivity using the CONN toolbox (https://www.nitrc.org/projects/conn/).

Neuroimaging Measures of Reward Response—For ventral corticostriatal network response to reward, we modeled functional connectivity among nucleus accumbens and

medial orbitofrontal ROIs for Win relative to Lose blocks in the Dice Guessing Task (Figures S1–S2). For dorsal corticostriatal network response to reward, we modeled functional connectivity among nucleus accumbens and dorsal anterior cingulate ROIs for Win relative to Lose blocks in the Dice Guessing Task.

Neuroimaging Measures of Executive Functioning—For anterior frontoinsular network response to executive functioning, we modeled functional connectivity among anterior insula and anterior-polar prefrontal regions for 2-back relative to 0-back blocks in the N-Back Task. For lateral frontoinsular network response to executive functioning, we modeled functional connectivity among anterior insula and lateral prefrontal regions for 2-back relative to 0-back blocks in the N-Back Task.

Group-Level Analyses—All variables were z-transformed before analyses. Correlations among neurocognitive variables were low to moderate, indicating that these variables reflect separable dimensions of neurocognitive functioning (Figure 1).

All available data were included in analyses; missing timepoints were omitted but participants with missingness were retained (their non-missing datapoints were included in analyses) to increase power and avoid biasing results. The glmmLasso and lme4 packages were used for penalized mixed effect models, with regularization using Least Absolute Shrinkage and Selection Operator (LASSO). For discussion of parameters and cross-validation, see Supplement and (Groll & Tutz, 2014). The ConsensusClusterPlus and cluster packages were used for clustering analyses.

Predicting anhedonic symptoms: Sample 1.: In Sample 1, a penalized mixed effects model identified neurocognitive variables that predicted future severity of anhedonia over the follow-up period, either directly (main effects) or by modulating stress-related changes in symptom severity (interactions with subjective stress score). Severity of daily anhedonia was regressed on prior-day stress, neurocognitive variables (behavioral reward performance and executive functioning factors, ventral and dorsal corticostriatal reward response, lateral and anterior frontoinsular executive functioning response), and the interactions between prior-day stress and neurocognitive variables. All neurocognitive variables were entered together into the model. Covariates were site, sex, age, prior-day anhedonia, and current and prior-day mania to isolate increases in anhedonia. Random intercepts and slopes (effect of stress) were nested within subject.

Predicting manic symptoms: Sample 1.: In Sample 1, a second penalized mixed effects model tested identified neurocognitive variables that predicted future severity of manic symptoms. Severity of daily mania was regressed on prior-day stress, neurocognitive variables, and the interactions between stress and neurocognitive variables. All neurocognitive variables were entered together into the model. Covariates were site, sex, age, prior-day mania, and current and prior-day anhedonia to isolate increases in mania.

Replication of symptom prediction: Sample 2.: The same penalized mixed effects models were repeated in Sample 2, omitting the site covariate (Sample 2 was collected at a single

site) and including the random effect of month (because daily diaries were clustered within months 0 and 3).

Clustering Analyses—We performed *k* means analyses to partition participants, in Sample 1 and then testing replication in Sample 2. Features included in clustering were neurocognitive variables that significantly predicted mania or anhedonia in penalized models in both Sample 1 and Sample 2. Values of k=2:n were tested, and the optimum *k* solution was identified using consensus clustering (Monti, 2003; see Supplement).

Follow-up penalized mixed effects models tested subgroup differences in anhedonic or manic symptom severity and stress-reactivity over time. These analyses complement models described above, but should not be considered independent given that subgroups were defined by neurocognitive variables that survived penalized models.

Supplementary Analyses—Exploratory and comparative analyses are reported in the Supplement. First, we report standard (without regularization) mixed effects models for comparison. Second, we report on penalized mixed models that include interactions among neurocognitive variables. Third, we report analyses that considered diagnostic status of the participant, or familial diagnostic history. Fourth, we report on analyses that predicted daily affect. Fifth, we repeat penalized models and clustering analyses in a pooled sample (combining across Samples 1 and 2). We chose to focus on independent samples in our primary analyses to support a test-replication approach. However, analyses in a pooled sample capitalize on larger sample size and provide a complementary perspective.

Availability of Data and Materials—Data from Sample 2 are available through the National Institute of Mental Health Data Archive (NDA) Collection C3598. Data from Sample 1 were collected prior to data sharing approvals, and are not publicly available.

Results

Description of the Samples and Data Quality

Description of the samples and data quality/confound checks can be found in Supplement, and Tables 1, S1–S3. Adherence to the daily diary procedure was acceptable. In Sample 1: out of 24 timepoints, MED=17, M=14, SD=9; in Sample 2: out of 42 timepoints, MED=20, M=21, SD=12. In both samples, adherence rate was not significantly associated with any experimental variables or age, qs=0.07–0.88. Including adherence in penalized models did not influence results, changes in Bs< 0.01, zs<0.02, ps<0.01.

Symptom distributions were inspected in the daily diary reports for both samples. Across participants in both samples, symptom fluctuations spanned the full scale ranges for symptoms of anhedonic depression (Bredemeier et al., 2010) or mania (Youngstrom et al., 2009), with higher severity of manic symptoms in Sample 1 (Supplement). Of note, symptom fluctuations should be interpreted dimensionally, and not as evidence for a clinical mood episode.

Neurocognitive Predictors of Anhedonia

In Sample 1, higher levels of subjective stress predicted increases in anhedonia the next day, B=0.13, z=2.10, p=0.03. In addition, there were significant moderated effects in which the relationship between stress and anhedonia was stronger for adolescents showing lower ventral corticostriatal reward response, B=−0.51, z=−6.34, p<0.01, or lower levels of reward performance behavior, B=−0.72, z=−10.01, p<0.01 (Figure 2). There was also a main effect in which adolescents with poorer behavioral executive functioning reported higher overall anhedonia, B=−2.57, z=−2.85, p<0.01, but lower stress-reactive change in anhedonia, B=0.27, z=3.45, p<0.01. Finally, adolescents showing lower anterior frontoinsular response to executive functioning reported higher overall anhedonia, B=−1.73, z=−2.03, p=0.04, and adolescents showing lower lateral frontoinsular response to executive functioning reported higher stress-reactive anhedonia, B=−0.24, z=−2.93, p<0.01 (Figure S3).

Replication was evaluated in Sample 2. Again, higher subjective stress predicted increases in next-day anhedonia, B=0.06, z=2.10, p=0.03. As in Sample 1, in Sample 2 the relationship between stress and anhedonia was stronger for adolescents showing lower ventral corticostriatal reward response, B=−0.16, z=−5.07, p<0.01, or lower levels of reward performance behavior, B=−0.25, z=−8.07, p<0.01. In addition, adolescents with poorer behavioral executive functioning reported lower stress-reactive change in anhedonia, B=0.15, z=4.85, p<0.01, but the main effect of poor behavioral executive functioning predicting higher overall anhedonia failed to reach significance, B=−0.41, z=−1.23, p=0.22. The effects of anterior and lateral frontoinsular executive functioning to predict anhedonia failed to replicate in Sample 2, Bs=−0.35 and 0.00 (Figure S3).

Neurocognitive Predictors of Mania

In Sample 1, higher levels of stress predicted increases in manic symptom severity the next day, B=0.12, z=1.98, p=0.04. Also, there were moderated effects in which the association between stress and manic symptom severity was stronger for adolescents with higher ventral corticostriatal reward response, B=0.53, z=6.89, p<0.01, lower levels of reward performance behavior, B=−0.20, z=−2.93, p<0.01, or poorer executive functioning behavior, B=−0.22, z=−3.18, p<0.01 (Figures 2, S4).

Replication was evaluated in Sample 2. Higher subjective stress failed to predict manic symptom severity, B=0.00, and neurocognitive effects failed to replicate, Bs=0.00.

Clustering

Clustering k means analyses were performed separately in Sample 1 and in Sample 2 to partition each sample based on neurocognitive features showing replicable prospective associations with symptoms. Features included: behavioral executive functioning, behavioral reward performance, and ventral corticostriatal reward response. Consensus clustering identified an optimal solution of five subgroups in both samples (Figures S5–S6). Quality of the partition for Sample 1 was 66%, and for Sample 2 was 59%.

Subgroups from clustering analyses are in Figure 3. In Sample 1, both Subgroups 1 and 2 exhibited poor behavioral executive function, but showed diverging patterns of high versus

low ventral corticostriatal reward response. Subgroups 3 and 4 were characterized by focal domains of reward hyposensitivity in the form of either low corticostriatal reward response or poor learning, but were average on other features. Subgroup 5 exhibited high behavioral performance. Similar patterns were observed for Sample 2.

Neurocognitive Clusters Predict Clinical Profiles

In Sample 1, subgroups 2, 3, and 4 reported higher stress-reactive anhedonia than other subgroups, Bs=0.47 – 2.01, zs=3.08–11.29, *p*s<0.01. Subgroup 1 reported higher anhedonia overall than other subgroups, B=2.61, z=2.56, *p*=0.01, higher stress-reactive manic symptoms, B=0.64, z=2.29, *p*=0.02, and non-significantly higher severity of manic symptoms overall, B=1.47, z=1.95, *p*=0.05, (Figure 4).

Replicating Sample 1 results, in Sample 2, subgroups 2, 3, and 4 reported higher stress-reactive anhedonia than other subgroups, Bs=0.56 – 0.72, zs=5.46–6.69, *p*s<0.01, (Figure 4). There were no Sample 2 differences in manic symptoms among subgroups, Bs=0.00.

Discussion

Identifying neurocognitive markers that predict mood pathology in adolescence may provide insight into risk and inform clinical translation. Towards this goal, we tested whether neurocognitive measures of reward processing and executive function predicted symptoms of mania or anhedonia in two samples of adolescents who varied in personal or family history of mood disorders. Results showed that neural and behavioral reward sensitivity and executive functioning behavior robustly predicted stress-reactive anhedonia (in both samples independently, and when samples were pooled; Supplement), and symptoms of mania (Sample 1, partial replication in pooled sample; Supplement). Clustering analyses identified neurocognitive risk phenotypes, i.e., subgroups of adolescents characterized by combined neurocognitive markers that showed distinct clinical profiles. Together, findings support the potential for neurocognitive markers to predict future health in adolescence, a developmental period characterized by both neurocognitive changes and heightened risk for onset of mood pathology.

In this study, reward processing abnormalities distinguished risk for different symptom dimensions and clinical profiles. Behavioral or neural hyposensitivities to reward were consistently associated with stress-reactive anhedonia, and adolescents characterized by reward hyposensitivities clustered into subgroups that reported unipolar symptom profiles over time. Reward hyposensitivity effects replicated across samples, and when samples were combined (Supplement). In contrast, adolescents showing ventral corticostriatal hypersensitivity to reward reported stress-reactive mania and clustered into a subgroup that reported a bipolar symptom pattern over time (but only in Sample 1). Overall, these findings align with evidence that some forms of reward hyposensitivity are markers of unipolar disorders, and some forms of reward hypersensitivity may be markers of bipolar disorders or symptoms (Alloy & Nusslock, 2019; Nielson et al., 2021). Neural systems involved in reward and stress have bidirectional influences (Corral-Frías et al., 2015), and exposure to reward can influence an individual’s responses to subsequent stress (Dutcher & Creswell, 2018). In addition, trait levels of reward sensitivity may moderate the association between

life stress and anhedonic depression (Nikolova et al., 2012). The results of the present study are consistent with this work, and suggest that mood is more strongly disrupted by daily stress among people with reward hypo- or hypersensitivities.

In contrast to specific associations between reward abnormalities and clinical profiles, adolescents who exhibited poor executive functioning reported worse mood symptom severity, especially anhedonia (with replication across independent and pooled samples; Supplement), and clustered into subgroups with either unipolar or bipolar trajectories. These results are consistent with evidence that common executive dysfunction is a general risk factor for adolescent mood pathology (Olvet et al., 2013; Vijayakumar et al., 2016). Executive dysfunction has been linked with broad deficits in emotion regulation (Joormann & Stanton, 2016) and general risk for internalizing disorders (Snyder et al., 2019). Future research will be useful to demonstrate whether executive dysfunction predicts mood or other symptoms in other psychiatric populations.

Results of clustering analyses highlight the value of evaluating combined patterns of neurocognitive abnormality, i.e., *neurocognitive phenotypes*. Several interesting findings emerged. First, adolescents showing neural and behavioral reward processing abnormalities tended to cluster separately. This pattern emphasizes that reward sensitivity is non-unitary (Berridge, 2018), and different forms of abnormal reward sensitivity may characterize subgroups even within the unipolar spectrum (Borsini et al., 2020). Second, adolescents showing reward abnormalities were characterized by average-to-poor executive functioning, and several subgroups with executive dysfunction reported relatively higher and/or more stress-reactive symptoms. These patterns suggest that adolescents who experience blunted or amplified responses to reward and also have difficulty regulating goal-directed behavior are more vulnerable to mood problems over time. Third, both reward hyper and hyposensitivity were associated with anhedonia, but in the context of bipolar versus unipolar clinical profiles. Phenotypes characterized by reward hyposensitivity (subgroups 2, 3, 4) reported elevated stress-reactive anhedonia, and a phenotype characterized by reward hypersensitivity (subgroup 1) reported elevated and sustained anhedonia (Sample 1). Together, results support that there is utility in identifying combined neurocognitive patterns that define naturally occurring subgroups which can then be described along multiple symptom dimensions.

It is important to note that this study yielded several null or non-replicable results across samples, including failure to replicate prediction of manic symptoms. Although our multi-sample approach is a strength, differences between samples may have contributed to replication failures. Specifically, Sample 1 (risk-enriched for lifetime history of mood disorders) reported higher severity and more variable manic symptoms than Sample 2 (risk-enriched for familial history of mood disorders). Therefore, failure to replicate prediction of manic symptoms may be driven by lower variance in such symptoms in Sample 2. Consistent with this interpretation, when penalized models were repeated combining data across samples (yielding a pooled sample with manic symptom severity and variability that was higher than Sample 2, but lower than Sample 1), partial replication of Sample 1 effects was observed (Supplement). Results that failed to replicate should be interpreted with

caution, and future work should extend to large high-risk samples over longer periods that may better capture e.g., onset of clinical mood episodes.

Limitations

There are several limitations to the present study. First, we measured neurocognitive features based on their theoretical relevance to adolescent mood pathology. However, other domains (e.g., threat response), systems (e.g., whole-brain measures), and units (e.g., molecular signaling) may also be of interest. Similarly, other subdimensions of executive functioning or reward sensitivity beyond those measured in this study may provide complementary information.

Second, we operationalized daily stress using subjective report, which may reflect both stress exposure and reactivity to stress (which in turn is associated with symptom severity, (Hammen, 2005)). We covaried prior-day mood symptoms to better isolate the effects of prior-day stress on next-day mood, but this cannot entirely distinguish stress from symptoms. Future research that evaluates objective and subjective measures of stress will better discriminate aspects of stress that may elicit mood changes.

Third, while this study described neurocognitive risk during a developmental period of vulnerability to mood pathology, the study did not evaluate developmental changes in risk. For example, exposure to high-intensity stress in childhood and adolescence may disrupt development of large-scale neurocognitive networks involved in reward sensitivity, stress regulation or cognitive control, culminating in neurocognitive risk (McEwen & Akil, 2020). Neurocognitive risk may also vary by puberty (Kaiser et al., 2022), pubertal hormones, or age-indexed social factors. Although this study controlled for age, suggesting that neurocognitive predictors are robust across adolescence, only by examining developmental processes and moderators in longitudinal design can we begin to answer these questions.

Fourth, our approach to define adolescence (as the period between puberty onset and the social-emotional transition to independence) yielded samples that spanned teen years into early twenties. There are other approaches for operationalizing this developmental period, and our sample could be characterized as capturing developmental periods of both adolescence and emerging adulthood. Future research that focuses on narrower age ranges could reveal new patterns of neurocognitive prediction that are specific to key windows of development (e.g., puberty onset, emerging adulthood).

Fifth, we emphasize the need for replication and further exploration of neurocognitive phenotyping approaches. Although prior simulation studies indicate sufficient power for clustering analyses with three to four features (Dalmaijer et al., 2003), exploration of higher-dimensionality clustering requires larger samples. In addition, we note that replication of a clustering solution across samples remains sensitive to sample size, even when statistical power to reliably partition data within a sample is adequate. In exploratory analyses that compared clustering solutions for independent versus combined samples, we observed notable variability in the stability of cluster assignments ranging from 88% (subgroup 1) to 68% (subgroup 4), suggesting that some neurocognitive phenotypes are more robust to sample size than others. Relatedly, it will be useful to compare the approach used here for

phenotyping, in which clusters are treated as discrete phenotypic subgroups, to alternative or complementary approaches e.g., that define an adolescent's phenotype according to their position in a multidimensional space defined by several neurocognitive features. Future studies comparing these approaches will provide insight into the nature of neurocognitive risk, and how to best aggregate information from multiple domains of neurocognitive functioning to predict adolescent health.

Conclusion

In conclusion, this study tested neurocognitive predictors of mood symptoms in adolescents. Abnormal reward responses and executive dysfunction predicted stress-reactive symptoms, and neurocognitive phenotypes emerged that exhibited distinctive symptom profiles over time. Future research should extend to understand how such phenotypes emerge and change over development and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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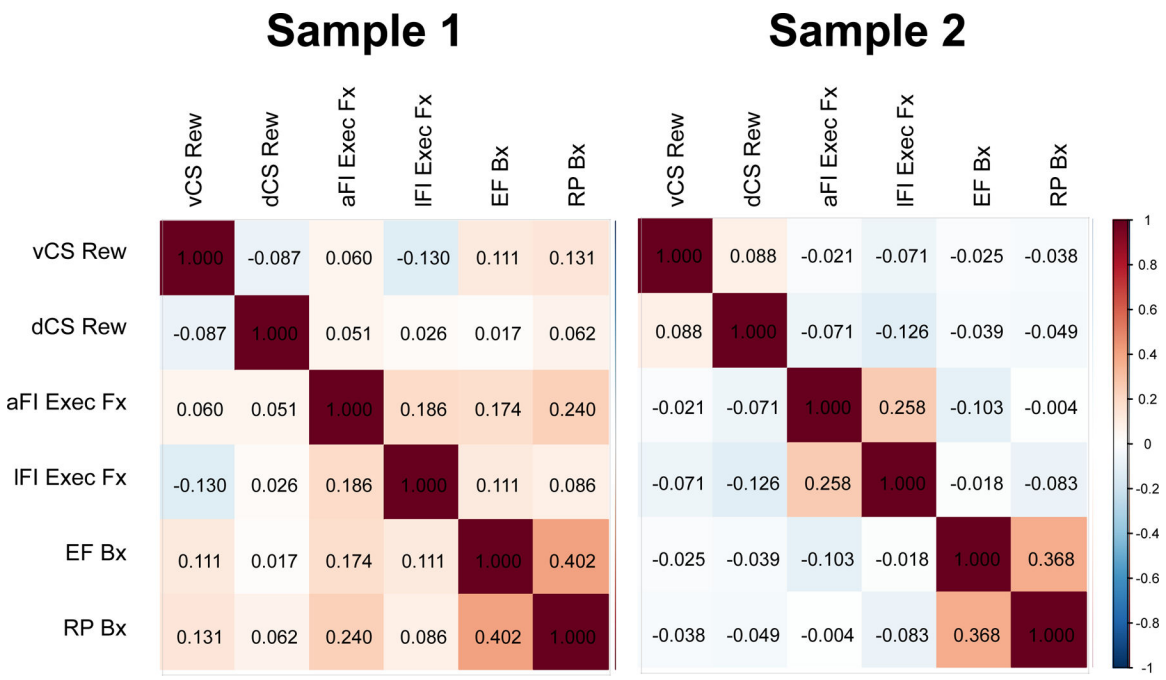

Figure 1. Correlations among neurocognitive variables.

Bivariate correlation matrices for neurocognitive variables in Sample 1 (*n*=73), Sample 2 (*n*=154). *Note:* vCS, ventral corticostriatal reward response, dCS, dorsal corticostriatal reward response, aFI Exec Fx, anterior frontinsular response to executive functioning, lFI Exec Fx, lateral frontinsular response to executive functioning, EF Bx, behavioral executive functioning, RP Bx, behavioral reward performance.

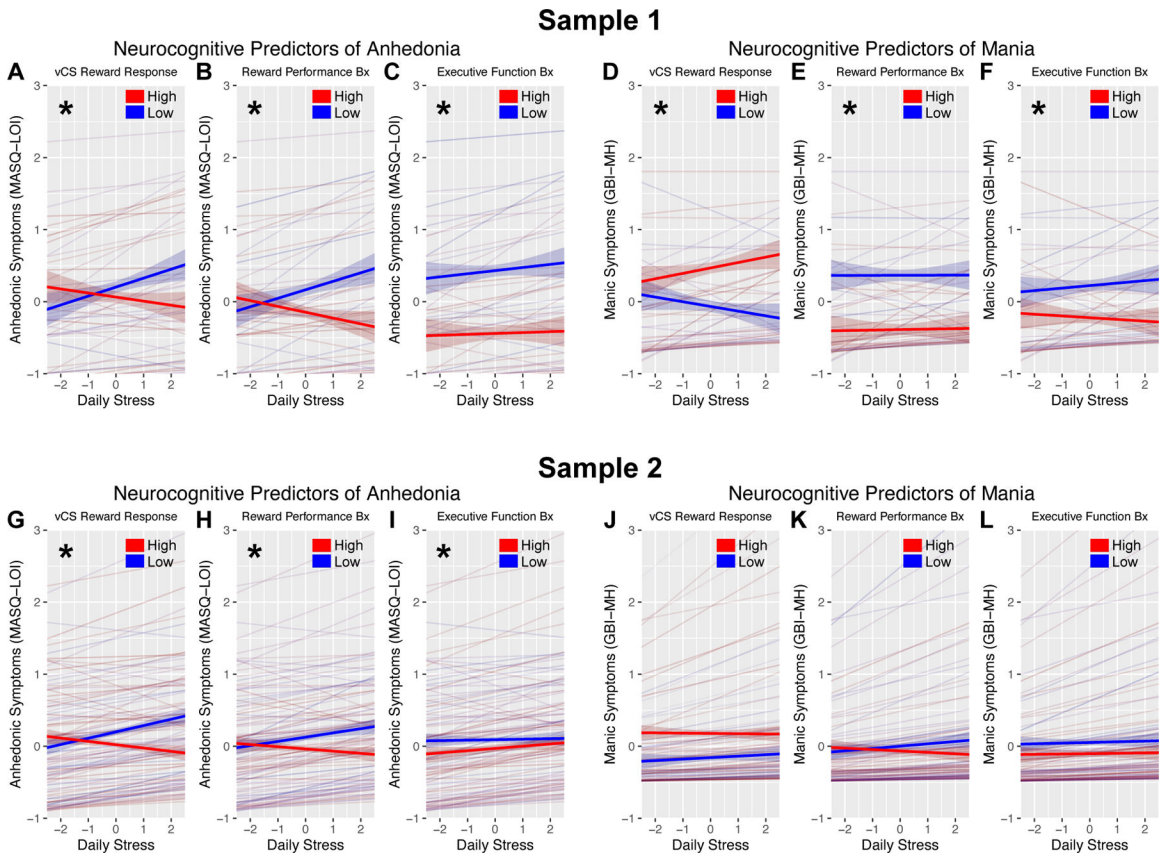

Figure 2. Neurocognitive predictors of stress-reactive anhedonic or manic symptoms.

In Sample 1, prospective associations between daily stress and symptoms of anhedonia, moderated by (**A**) ventral corticostriatal (vCS) reward response (**B**) behavioral reward performance, or (**C**) behavioral executive functioning. In Sample 1, prospective associations between daily stress and symptoms of mania, moderated by (**D**) ventral corticostriatal (vCS) reward response (**E**) behavioral reward performance, or (**F**) behavioral executive functioning. In Sample 2, prospective associations between daily stress and symptoms of anhedonia, moderated by (**G**) ventral corticostriatal (vCS) reward response (**H**) behavioral reward performance, or (**I**) behavioral executive functioning. In Sample 1, prospective associations between daily stress and symptoms of mania, moderated by (**J**) ventral corticostriatal (vCS) reward response (**K**) behavioral reward performance, or (**L**) behavioral executive functioning. *Note:* MASQ-LOI, Mood and Anxiety Symptom Questionnaire – anhedonic Loss of Interest subscale; GBI-MH, General Behavior Inventory – Mania/Hypomania subscale. Displayed are fit lines at low (blue, −1.5 standard deviations from mean) or high (red, +1.5 standard deviations from mean) levels of the neurocognitive measure of interest. *p<0.05 main or moderated effects, penalized mixed effects models.

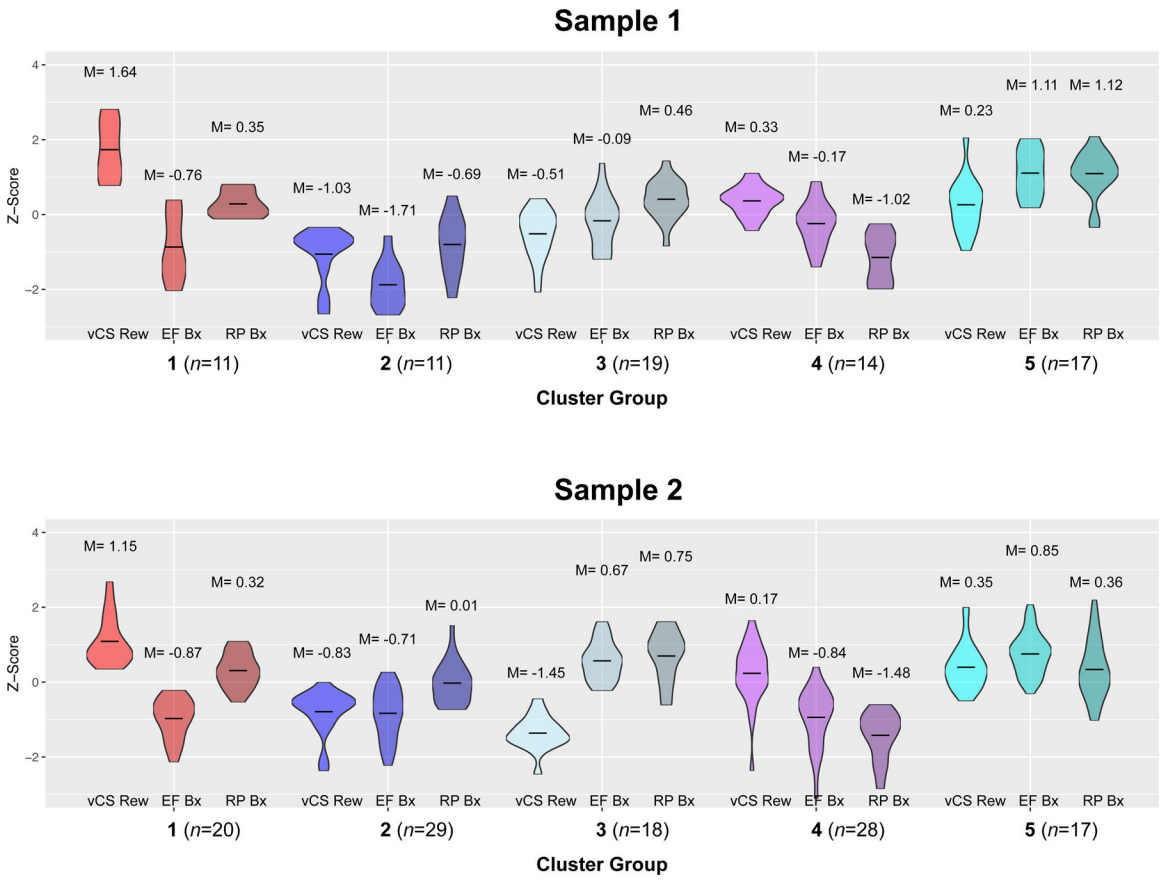

Figure 3. Neurocognitive phenotypes.

Consensus clustering with *k* means applied independently to Sample 1 and Sample 2 identified five subgroups of adolescents in each sample on the basis of combined neurocognitive features that survived penalized regression. Neurocognitive features: ventral corticostriatal (vCS) reward response, behavioral executive function (EF Bx), and behavioral reward performance (RP Bx).

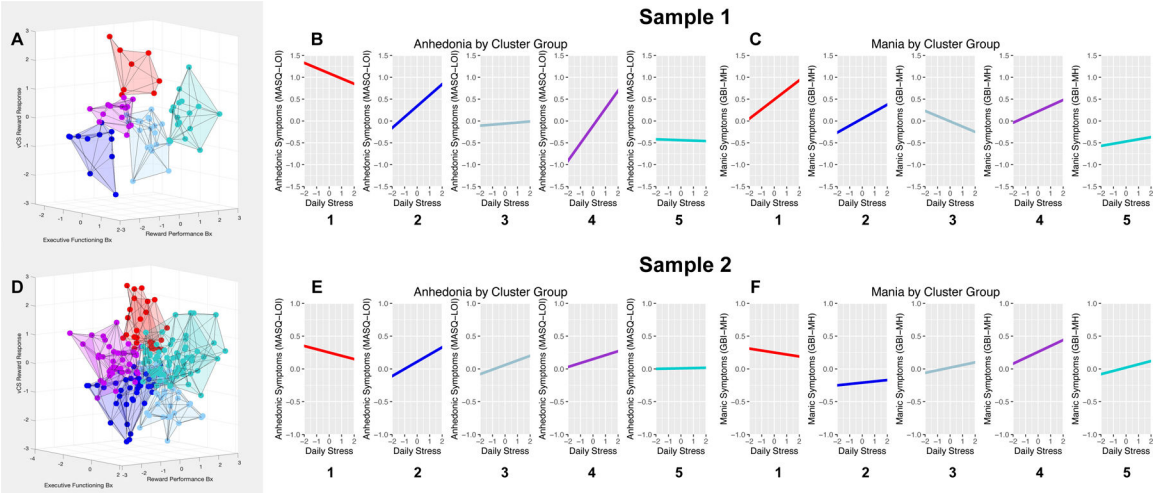

Figure 4. Neurocognitive phenotypes and related symptom profiles.

In Sample 1, (**A**) neurocognitive phenotypes defined by clustering analyses, and **(B-C)** prospective associations between daily stress and symptoms of anhedonic depression or mania for each phenotype subgroup. In Sample 2, (**D**) neurocognitive phenotypes defined by clustering analyses, and **(E-F)** prospective associations between daily stress and symptoms of symptoms of anhedonic or mania. *Note:* MASQ-LOI, Mood and Anxiety Symptom Questionnaire – anhedonic Loss of Interest subscale; GBI-MH, General Behavior Inventory – Mania/Hypomania subscale. For display, Sample 1 y axis scaled to +/− 1.5 standard deviations from mean z-score (0), Sample 2 y axis scaled to +/− 1 standard deviations from mean z-score (0).

Table 1.

Summary of Demographic Characteristics and Clinical and Familial History

	Sample 1 *n* = 73	**Sample 2 *n* = 154**
	M (SD)	M (SD)
Age (years)	19.22 (2.49)	16.46 (1.95)
Pubertal Development Scale	3.72 (0.38)	3.47 (0.56)
Sex	%	%
Female	56.16	58.44
Male	43.84	41.56
Gender	%	%
Cisgender Woman	53.42	53.90
Cisgender Man	43.84	38.31
Other	2.74	7.79
Ethnicity	%	%
Hispanic or Latine	21.92	9.09
Non-Hispanic and Non-Latine	78.08	90.91
Race	%	%
Asian	16.44	3.90
Biracial or More than One Race	9.59	11.69
Black or African American	4.11	1.30
Native Hawaiian	0	0
Native American	0	0
White	67.12	82.47
Other	2.74	0.65
Mood Symptoms at Baseline	M (SD)	M (SD)
Mood and Anxiety Symptom Questionnaire-Loss of Interest Scale (7-item)	20.01 (7.93)	15.00 (5.70)
General Behavior Inventory-Mania/Hypomania Scale (10-item)	4.64 (5.10)	3.48 (3.86)
First-degree Family History of Mood Disorders	%	%
Unipolar Disorders	--	42.86
Bipolar Disorders	--	18.83
No Mood Disorders	--	38.31
Lifetime Mood Disorders	%	%
Unipolar Disorders	56.16	19.48
Major Depressive Disorder	30.14	16.88
Persistent Depressive Disorder	26.03	2.60
Bipolar Disorders	12.33	3.25
Bipolar I Disorder	4.11	1.30
Bipolar II Disorder	1.37	0.65
Bipolar Disorder Not Otherwise Specified	6.85	1.30
No Mood Disorders	31.51	77.27

	Sample 1 *n* = 73	**Sample 2 *n* = 154**
Subclinical Depressive Episode	8.22	14.94
Subclinical Manic/Hypomanic Episode	0	1.95

Note. Lifetime mood diagnoses evaluated with the Structured Clinical Interview for the DSM5 Research Version. Familial history was evaluated in Sample 2 at the time of recruitment. Two participants in Sample 1 reported Major Depressive Disorder with mixed features. For detailed demographic and clinical characteristics, see Tables S1–S2.