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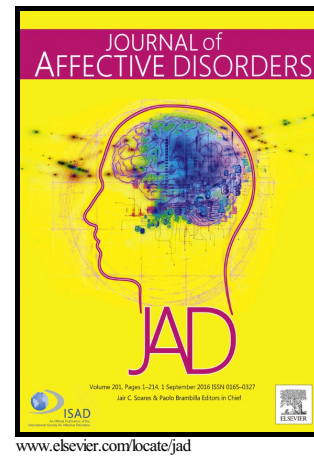
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Prenatal Maternal Mood Patterns Predict Child Temperament and Adolescent Mental Health

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Abstract

Background

This study quantifies the dynamics of maternal mood focusing on unpredictability, and to assess if greater unpredictability of prenatal maternal mood predicts child temperament and internalizing symptoms through early adolescence.

Methods

The association between prenatal mood predictability and child internalizing symptoms were assessed in two longitudinal cohorts (N's = 227 and 180). Maternal mood was assessed repeatedly during pregnancy as early as 15 weeks' gestation. Predictability of maternal mood was calculated by applying Shannon's entropy to the distribution of responses on mood questionnaires. Maternal reports of child negative affectivity (a predictor of later internalizing) were collected at 6, 12, 24 months and 7 years of age. Child self-reports of anxiety symptoms were collected at 10 years and reports of depression symptoms at 13 years.

Results

Fetal exposure to more elevated maternal mood entropy predicted higher levels of child negative affectivity at 12 months (r = .36; p < 01), 24 months (r = .31; p < 01) and 7 years (r = .32; p < 01) of age. In addition, children exposed to higher prenatal maternal mood entropy, reported higher levels of anxiety symptoms at 10 years (r = .24; p < 01) and elevated depressive symptoms at 13 years (r = .29; p < .01). These associations persisted after adjusting for maternal pre and postnatal mood valence (e.g. depression levels) and for other relevant demographic characteristics.

Conclusions

Our findings provide strong support for the notion that patterns of maternal mood influence the developing brain. More specifically, they suggest that prenatal maternal mood predictability may be a critical predictor of developmental mental health trajectories and should be considered when assessing early life influences on lifespan mental health.

Keywords

Prenatal, Postpartum, Pregnancy, Depression, Anxiety, Temperament, Child Development, Entropy, Internalizing Disorders, Adolescence, Emotion Regulation

Introduction

Few families in the United States escape the burden imposed by mental illness. The lifetime prevalence among adolescents in the US is estimated to be 46.3% for any mental health disorder and 21.4% for severe disorders (Merikangas et al., 2010). The National Comorbidity Survey Replication study estimated that exposure to early-life adversity may account for 32.4 percent of psychiatric disorders (Green et al., 2010). Prenatal and early life stress and trauma exposures have been linked to a broad range of mental health conditions including schizophrenia, depression, anxiety, and posttraumatic stress disorder (Gilbert et al., 2009; Heim and Nemeroff, 2001; Khashan et al., 2008; Kingsbury et al., 2016). Evidence from human studies (Qiu et al., 2015; Slopen et al., 2012; Woon and Hedges, 2008) and from animal models (Avishai-Eliner et al., 2002; Chen and Baram, 2016; Gunnar et al., 2015; Spinelli et al., 2009) further suggests that exposure to prenatal and early-life adversity may be causally related to brain changes underlying the risk for psychopathology.

Given the accumulating evidence relating prenatal maternal psychological distress to risk for mental health disorders and their underlying neural mechanisms (Babenko et al., 2015; Buss et al., 2010; Huizink et al., 2002; Khashan et al., 2008; Lebel et al., 2015), an important next step is the identification of specific components of maternal signals that shape the developing brain. Previous work indicates that *patterns* of maternal sensory input, particularly fragmented or unpredictable signals, influence the maturation of systems governing emotional regulation in the offspring's developing brain (Baram et al., 2012; Davis et al., in press). For example, rodents that are exposed to unpredictable patterns of maternal-derived sensory input during postnatal life, exhibit diminished cognitive function and increased anhedonia beginning in adolescence (Brunson et al., 2005; Ivy et al., 2010; Molet et al., 2016). Importantly, these effects are independent of the quantity of these maternal behaviors, underscoring the importance of *patterns* of unpredictability in shaping the immature brain.

Analysis of intraindividual patterns in behaviors and attitudes is rooted in personality psychology (c.f. Fiske and Rice, 1955; Mischel and Shoda, 1995) and has been most commonly characterized as either intraindividual variability in item scores on a questionnaire or intraindividual fluctuations across situations and time (Eid and Diener, 1999; Penner et al., 1994). Further, for the past 50 years, emotion theory has recognized that mood patterns, independent of level, are central components of affective experience in their own right (Larsen and Diener, 1987; Wessman and Ricks, 1966). There exist a range of techniques for studying emotion dynamics which include examination of patterns over time (e.g. weeks or months) and dynamics at a single point in time, capturing a snapshot of emotional experience (Kuppens and Verduyn, 2015). Intraindividual variability in mood and affect has implications for understanding both clinical and non-clinical emotional states and traits. For example, more extreme variability in mood has been linked to higher levels of affect intensity (Larsen and Diener, 1987), more self-complexity (Campbell et al., 1991), lower self-esteem (Kuppens et al., 2007) and to a range of personality traits including neuroticism, extraversion and sensation seeking (Hepburn and Eysenck, 1989; Larsen and Kasimatis, 1990). Increased mood variability across hours or days, also has been linked to risk for bipolar disorders (Bonsall et al., 2012; Depue et al., 1981), clinical and sub-clinical depression (Kuppens et al., 2007; Thompson et al., 2011), and anxiety disorders (Bowen et al., 2006). These theoretical perspectives and the empirical findings highlighting the link between individual differences in mood variability and risk for psychopathology are consistent with a

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broader growing literature that identifies deficits in emotion regulation as a transdiagnostic factor in mental health and in mood disorders in particular (Aldao et al., 2010; Fernandez et al., 2016; Kring and Sloan, 2010).

We examine here whether unpredictability of prenatal maternal mood might influence the developing fetus. We characterize unpredictability in mood using a measure of normalized entropy. Specifically, we examine whether maternal prenatal mood entropy predicts child temperament and internalizing symptoms over and above the well-established relations with *levels* of maternal mood in two independent, prospective, longitudinal cohorts of women and their children (Ns = 227 and 180) who were followed beginning at 15 weeks' gestation through early adolescence.

Materials and Methods

Overview of Data Collection

Participants were recruited from affiliated clinics from one of two large university medical centers in Southern California. Recruitment criteria included: 1) singleton pregnancy 2) over the age of 18, 3) English speaking 4) non-smoking, and 5) absence of any condition that could dysregulate neuroendocrine function. Participants in both cohorts were recruited during the first trimester of pregnancy and participated in four to five prenatal study visits (See Figure 1). In addition, the mother-child pairs participated in postnatal visits that began as early as 6 months through 13 years of age. Cohort 1 consisted of 227 mother-child pairs and Cohort 2 of 180 pairs. The number and distribution of both pre- and postnatal visits differed by cohort and can be seen in Figure 1. Characteristics of mother-child pairs are presented in Table 1. At each of the prenatal study visits mothers reported on demographics and mood through questionnaires and structured interviews. At each of the postnatal visits, the mothers completed assessments of developmentally-appropriate predictors of risk for internalizing disorders and also reported on their own mood. Children reported on their own anxiety symptoms at age 10 and on their depressive symptoms at age 13. Research was approved by the responsible institutional review board and all mothers provided written informed consent after the procedures had been fully explained. In addition, children provided assent at the study visits at 7, 10 and 13 years of age.

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Characterization of Mood Unpredictability

Parameters Assessed

Depressive Symptoms Maternal depressive symptoms were characterized using the nine-item form of the Center for Epidemiologic Studies Depression Scale (Santor and Coyne, 1997) during the prenatal visits and at all postnatal visits except for 7-years (see Figure 1). Responses to each of the nine items in this measure were recorded on a 4-point Likert scale, with a range of 0 to 3. The final score could span from 0 to 27, with a higher score indicating greater impairment. This measure has been extensively used, and published studies demonstrate good internal consistency and validity in both pregnant women and in the general population (Marcus et al., 2003; Santor and Coyne, 1997). At the 7-year assessment maternal depressive symptoms were assessed with the Beck Depression Inventory (BDI; Beck et al., 1961). The BDI is a 21-item instrument that exhibits high internal consistency (alphas >.81) in both psychiatric and non-psychiatric populations (Beck et al., 1988). In addition, it possesses significant validity in detecting the differences between depressed and non-depressed individuals (Richter et al., 1998).

State Anxiety State anxiety was measured with the 10-item state anxiety subscale of the State-Trait Personality Inventory (Spielberger, 1979). Various anxiety-related adjectives were rated on a 4-point scale. This brief measure has demonstrated good psychometric properties when used in pregnant and non-pregnant populations (Glynn et al., 2008; Spielberger, 1979).

Pregnancy Specific Anxiety A 10-item scale was used to address a woman's feelings about her health during pregnancy, the health of her baby, and her feelings about labor and delivery (Rini et al., 1999). Answers are given on a 4-point scale and included items such as: "I am fearful regarding the health of my baby," "I am concerned or worried about developing medical problems during my pregnancy." This measure exhibits good internal validity (Glynn et al., 2008; Rini et al., 1999) and is predictive of birth and child development outcomes (c.f.Buss et al., 2010; Dunkel Schetter and Glynn, 2011)).

Perceived Stress The Perceived Stress Scale (Cohen et al., 1983) was used to assess the extent to which situations in one's life are appraised as stressful. This instrument includes questions regarding

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how often women felt they were able to successfully manage day-to-day problems and hassles and how often they felt nervous or stressed. Responses are given on a 5-point Likert scale. The scale is predictive of a wide range of physical and mental health outcomes (Cohen et al., 1993; Hewitt et al., 1992) and demonstrates good reliability (Cohen et al., 1983).

Calculation of Mood Predictability

To characterize predictability or consistency of mood, we calculated an entropy score by applying Shannon's entropy to the distribution of responses on the four mood questionnaires individually at each visit (Cover and Thomas, 2006). Shannon's entropy is associated with the concept of information and the efficiency with which messages can be sent along binary communication channels. The formula is given here:

$$ENT = -\sum_{e \in E} p_e \log_2(p_e)$$

In this formula, E denotes the range of possible responses for items on a mood scale (say 0 to 3 on the PSS) and p_e represents the proportion of responses in each category. This application involves a quantification of unpredictability of the item-by-item responses to assessments of mood states. The responses at a single assessment are tabulated over the items within each scale into probability distributions based on the relative frequency of each response choice, and these distributions represent empirical estimates of the propensity of a study subject to respond across items in a consistent way. In this sense, mood entropy quantifies the degree of predictability of the item-specific response. A participant who generally reports never worried or always secure on the STAI, for example, would be considered very predictable and thus have a very low entropy score, whereas a woman who completes the STAI items entirely at random would have a very high entropy score. Table 2 presents an example of the responses of a single participant to the STAI items and how these are used to compute the entropy for that individual on that scale. The entropy measure for a scale ranges from zero (perfectly predictable) to a maximum value that depends on the number of points on the scale. To facilitate application of the approach across the different mood questionnaires we normalized the entropy score by expressing it as a percentage of the maximum value. Thus normalized entropies range from 0 to 100.

Test of Discriminant Validity

It is possible that rather than reflecting something about mood regulation, that the measure of entropy reflects instead a general tendency to answer questionnaire items in an unpredictable or inconsistent manner. To evaluate this alternate explanation, we calculated an entropy score from a scale assessing physical activity during the prenatal period. This 10-item Likert scale asks participants to rate their average time spent on various types of physical activities including: "hours per day sitting" and "hours per day walking." Answers are given on a 12-point scale that ranges from 1 (one or less hours) to 12 (12 or more hours). This scale shows similar psychometric properties to the mood indices.

Test of Convergent Validity

We additionally tested the convergent validity of our mood entropy measure by examining its association with affective instability, a time-based, momentary measure of mood variability. In a third ongoing, prospective, longitudinal study of pregnant women (n = 151), mood entropy scores were derived exactly as described above from questionnaire data obtained at a laboratory visit at 15 weeks' gestation. In addition, an experience sampling (Csikszentmihalyi and Larson, 1987) or ecological momentary assessment (EMA; Stone and Shiffman, 1994) protocol was then completed within two weeks of the laboratory visit. These momentary mood assessments were delivered eight times a day for three consecutive days on a semi-random schedule via smart phone application (mEMA, Ilumivu). Daily mood variability scores were calculated from EMA measures parallel to those questionnaires comprising the mood entropy index (CESD-VAS-VS:Moullec et al., 2011; PSS-4:Cohen and Williamson, 1988; anxious mood subscale of POMS-15:Cranford et al., 2006) using the standard root mean square successive difference (RMSSD; see Ebner-Priemer et al., 2009; Jahng et al., 2008; Solhan et al., 2009). RMSSD scores for each measure for each day were averaged. For ease of interpretation, a single RMSSD index was calculated by averaging standardized RMSSD scores across the three measures. RMSSD index scores did not vary as a function of compliance (total number of assessments completed; *r* = -.04, ns).

Characterization of Risk for Internalizing Disorders

Negative Affectivity

Child negative affectivity was assessed at 6 and 12 months with the Infant Behavior Questionnaire (IBQ; (Gartstein and Rothbart, 2003), at 2 years with the Early Childhood Behavior Questionnaire (ECBQ; (Putnam et al., 2006) and at 7 years with the Children's Behavior Questionnaire (CBQ; Rothbart et al., 2001). These scales contain developmentally appropriate, maternal report measures of Negative Affectivity, a temperament dimension which predicts later internalizing symptoms (Gulley et al., 2016). These instruments were developed specifically to reduce the possibility of maternal reporting bias by asking about specific behaviors in defined situations, rather than asking for judgments about child temperament or behaviors. Responses on these scales range from 1 (never) to 7 (always). These measures exhibit good internal reliability and validity (Goldsmith and Campos, 1990; Worobey and Blajda, 1989).

Child Report of Anxiety Symptoms

Children completed the trait anxiety (T-Anxiety) scale from the State-Trait Anxiety Inventory for Children (STAIC; Spielberger et al., 1973) as part of a structured interview. This 20-item scale is designed to assess anxiety-proneness. The interviewer read 20 statements (e.g., "I worry about making mistakes," "I worry about things that may happen"). After each statement, the child was asked to decide whether the statement was "hardly ever," "sometimes," or "often" true for him/her. These responses are assigned values of 1, 2, and 3, respectively, allowing sum scores to range from 20 to 60. The STAIC has good test-retest reliability and internal consistency (Spielberger et al., 1973). It also exhibits good predictive (Seligman et al., 2004) and concurrent validity, with STAIC trait anxiety scores correlating at $r = .75$ and .63 with scores on the Children's Manifest Anxiety Scale (Castaneda et al., 1956) and General Anxiety Scale for Children (Sarason et al., 1960), respectively.

Adolescent Report of Depressive Symptoms

The 12-item short self-report version of the Children's Depression Inventory (CDI 2; Kovacs, 2011) was used to assess adolescent depressive symptoms. The interviewer read 12 sets of three statements, and the child was asked to indicate which of the statements best described him or her in the past two weeks (e.g., "I am sad once in a while," "I am sad many times," or "I am sad all the time," scored 0, 1, and 2 respectively). Scores on the CDI can range from 0 to 24. The CDI has been validated and used extensively in previous research involving children and adolescents (Kovacs, 2011; Stockings et al., 2015; Timbremont et al., 2004)

Data Analysis

When child age at assessment overlapped (See Figure 1), data from the two cohorts were combined in analyses. Bivariate correlations were used to assess relations between mood entropy and child outcomes. Partial correlations were then used to assess plausible third variable explanations (See Table S1). Potential covariates in these analyses included: socioeconomic status (a composite was created by standardizing maternal education level and household income and then averaging the two), race/ethnicity (self-identified), maternal age, cohabitation with father during pregnancy, child sex, gestational age at birth, birth order, and child age at assessment. The following variables exhibited an association $p < .05$ with both the predictor and outcomes and so were included as covariates in all analyses: maternal age, socioeconomic status, cohabitation, gestational age at birth and child age at assessment. In addition, because mood entropy was modestly correlated with mood levels (range .26 to .69), and because pre and postnatal maternal mood states have been demonstrated to influence temperament and internalizing symptoms, we included both pre and postnatal mood levels in the models. Last, linear regression models tested whether any prenatal mood entropy effects that were detected could be accounted for by postnatal maternal mood entropy. In these models prenatal mood entropy and postnatal mood entropy at the time point of the child assessment both were entered simultaneously into the models as predictors.

Our planned analyses include bivariate correlations of entropy with child negative affectivity and internalizing symptoms and partial correlations adjusting for plausible confounders. Thus, we test twelve correlations. We use the false discovery rate approach (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001) to adjust for the multiple comparisons.

Because of the well-established relations between child temperament and risk for psychopathology, as a secondary aim, we examined whether child negative affectivity mediated any associations between prenatal mood entropy and later child anxiety and depressive symptoms. Specifically, four separate mediation models were utilized to evaluate potential indirect effects of maternal prenatal mood entropy (independent variable) as a predictor of child anxiety and adolescent depressive symptoms (dependent variables) through infant and child negative affectivity (mediators). Models were evaluated with the bootstrapping procedure described in Preacher & Hayes (2004), using 5000 bootstrap samples and a 95% bias-corrected confidence interval.

Results

Mood Entropy

Mood entropy was stable across gestation for both cohorts with no reliable patterns of differences based on gestational time point for any of the four measures. The means across the four measures ranged from 48.5 to 59.4 and the variances of the entropy scores also were similar for each of the four mood measures (sd's ranged from 17.6 to 24.9). For each of the four scales, average correlations of mood entropy across gestation ranged from .44 to .54. Because of these findings, a single mood entropy index was created by averaging mood entropy scores within each scale and then averaging these gestational averages (correlations among these averages ranged from .34 to .53). A similar strategy was employed to create a single mood level composite for the prenatal period and the mood measures were similarly standardized and averaged at each of the postnatal assessments.

Test of Discriminant Validity: Mood Entropy or Entropy in Response Style?

The correlation between mood entropy and entropy calculated from the physical activity questionnaire was .08 (ns). However, unlike mood entropy, entropy in responses to the physical activity

questionnaire was not predictive of maternal reports of child negative affectivity (r's ranged from .01 to .10, all ns) nor of child self-reports of anxiety and depressive symptoms (r's = -.03 and .07 respectively, both ns).*Prenatal Maternal Mood Entropy and Maternal Report of Negative Affectivity*

Higher maternal prenatal mood entropy was predictive of increased child negative affectivity at 6 (r = .23, p < .01) and 12-months of age (r = .36, p < .01; See Figure 2). These positive associations also were observed at 24 months (r = .31, p < .01) and at 7 years of age (r = .32, p < .01; See Figure 2). In addition, the relations at 12 months (partial *r* = .18; p < 05), 24 months (partial *r* = .19; p < 05) and 7 years (partial *r* = .14; p < 05) persisted after adjustment for gestational age at birth, child age at assessment, socioeconomic status, cohabitation with the child's father, maternal age, prenatal mood level and concurrent postnatal mood level. The association between mood entropy and negative affectivity at 6-months of age, did not survive adjustment for covariates (partial r = -.06; p = .41).

Prenatal Mood Entropy and Child Report of Anxiety and Adolescent Report of Depressive Symptoms

Higher prenatal mood entropy was associated with increased child report of anxiety symptoms at age 10 (r = .24; p < 01; See Figure 3a) and with adolescent reports of depressive symptoms at age 13 (r = .29; p < .01; See Figure 3b). Similar to the relations between mood entropy and maternal reports of fearful temperament, the effects persisted after adjusting for gestational age at birth, child age at assessment, socioeconomic status, cohabitation with the child's father, maternal age, prenatal mood level and concurrent postnatal mood (partial *r's* = .24, p < 01 and .17, p < .05, respectively).

Multiple Comparisons

The six bivariate correlations of entropy with negative affectivity and internalizing symptoms are all significant with p < .01. Five of the six partial correlations tested are significant with p < .05. A false discovery rate with 5% false discoveries identifies all 11 of the significant correlations as discoveries.

Test of Convergent Validity

Prenatal mood entropy scores were positively associated with RMSSD affective instability scores, *r* = .42, *p* < .001. In other words, women with higher levels of mood entropy exhibited higher levels of affective instability across three days in the course of their daily lives.

Test of the Unique Contributions of Prenatal Mood Entropy

Table 3 contains summaries of the regression models in which both pre and postnatal mood entropy were modeled together. At each time point (12 and 24 months, 7 years), both pre and postnatal maternal mood entropy were independently and positively associated with maternal report of child negative affectivity. For child report of state anxiety, pre and postnatal entropy each dropped to the trend level of statistical significance. Last, for adolescent report of depressive symptoms, both pre and postnatal mood entropy remained statistically significant predictors in the model.

Testing Relations between Temperament and Internalizing Symptoms

As expected, infant and child negative affectivity was positively associated with child anxiety symptoms (See Table S1). However, models testing mediation failed to reveal any significant indirect effects of prenatal mood entropy on child anxiety and adolescent depressive symptoms through infant or child negative affectivity (see Table S2 for details).

Discussion

These results identify mood entropy as a novel marker of prenatal maternal mood dysregulation that exhibits persisting associations with risk for internalizing symptoms in offspring. Specifically, we demonstrate that mood entropy predicts maternal reports of negative affectivity in infancy and childhood as well as child and adolescent self-reports of anxiety and depressive symptoms. Importantly, the effects of prenatal mood entropy were independent of pre and postnatal maternal mood *levels,* other well-established contributors to child mental health (Monk et al., 2012; O'Connor et al., 2003; Pearson et al., 2013; Sandman et al., 2015) and these effects appear to be independent of postnatal mood entropy. There are three critical components of the methodology that increase our confidence in the importance of this new indicator of mood dysregulation. First, the results cannot be attributed to maternal characteristics associated with questionnaire response style. Identical entropy values calculated from a prenatal questionnaire assessing physical activity, which has similar psychometric properties to the mood questionnaires were not predictive of child internalizing symptoms. Second, mood entropy was positively associated with mood variability measured across

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days in the field with ecological momentary assessment techniques.   Third, the results reflect not only maternal report of fearful temperament, but child self-report of anxiety and depressive symptoms as well, which further suggests that this is not simply an artifact of maternal reporting style or bias.

Because negative affectivity is a temperament dimension that represents a well-established risk factor for internalizing problems (Dougherty et al., 2010; Dar and Iqbal, 2015; Markon et al., 2005; Sayal et al., 2014; Tortella-Feliu et al., 2010), as a secondary aim, we tested whether the association between mood entropy and child anxiety and adolescent depressive symptoms might be mediated partially or fully through temperament in infancy and childhood.   Here we replicate previously established relations between temperament and psychopathology risk – negative affectivity in infancy and childhood did predict later internalizing symptoms. However, the results of our analyses did not support the supposition that temperament plays a role in the causal pathway linking mood entropy to child psychopathology risk. It may be the case that these null findings are veridical. However, it also is possible that we did not detect relations because these children represent relatively low-risk, typically developing individuals or because these relations would not be revealed without consideration of moderated-mediation (Kiel and Buss, 2011; Dunkel Schetter and Glynn, 2011). Temperament-psychopathology relations are often not detected without careful consideration of the moderating factors associated with contextual risk (Degnan et al., 2010; Hentges et al., 2015; e.g. peer groups, Frenkel et al., 2015; father absence, Boyce et al., 2006); stress exposures, Gulley et al., 2016), the examination of which extends beyond the scope of this study.

Although it is clear that maternal mood entropy is a consistent predictor of child mental health risk, it is less clear what this index reflects about women's experience of mood or emotion regulation. The two primary possibilities related to emotional experience that could account for variation in mood entropy are lability of emotions and alexithymia, both of which are plausible and not mutually exclusive. Women who exhibit high mood entropy profiles may experience wide variations in their emotional experiences, it also possible that high mood entropy is indicative of a lack of emotional clarity or an inability to properly differentiate emotions (Boden et al., 2013). Our data linking mood entropy to mood lability measured over days with EMA methods support the argument that mood entropy does reflect in part individual differences in mood variability.   Both mood variability and

alexithymia are predictive of clinical and subclinical psychopathology (Depue et al., 1981; Frewen et al., 2008; Kim et al., 2016; Thompson et al., 2011) and future research will have to determine further, the precise nature of the emotional dysregulation associated with mood entropy.

At this time, the mechanism underlying the association between prenatal maternal mood entropy and child internalizing remains unknown. Identification of such a mechanism represents a similar challenge to that currently faced by the literature documenting associations with *levels* of prenatal maternal distress (e.g. how does prenatal maternal depression, stress or anxiety influence the developing fetus). However, advances in studies examining the mechanisms underlying maternal prenatal distress levels and child outcomes may serve as an initial roadmap for domains to consider that may be relevant to mood entropy and these include: neural, endocrine, immune, epigenetic and vascular pathways (Christian, 2014; Hilmert et al., 2014; O'Donnell et al., 2009; Shea et al., 2008). We are aware of only one study to date that has examined the physiological signature associated with intraindividual mood variability. Koval et al. (2013) showed that higher levels of affective instability were predictive of lower heart rate variability in a sample of male and female undergraduates. This is notable because individual differences in vagally-mediated heart rate variability are associated with emotion regulation and are predictive of cardiac and psychological health outside of the perinatal period (Thayer et al., 2012). Further, a few studies have shown that reduced maternal prenatal heart rate variability is associated with increased maternal depressive symptoms (Rouleau et al., 2016; Shea et al., 2008) and experimental manipulation of maternal respiratory sinus arrhythmia results in alterations in maternal-fetal heart rate synchronization (Van Leeuwen et al., 2009). Clearly, these findings point to the need to determine whether mood entropy is associated with maternal heart rate variability or other potential biological mechanisms in the context of pregnancy.

The strengths of this study reside in the examination of the associations between prenatal maternal mood entropy and risk for child internalizing prospectively into adolescence in two prospective cohorts. Our confidence in the findings are greatly increased by the fact that we observe these associations with both measures of maternal report of child temperament as well as with child reports of their own anxiety and depressive symptoms. Further, careful characterization of mood levels and inclusion of these in our statistical models support the role of mood entropy as a novel predictor

of child internalizing symptoms, which is independent of mood level or affective valence. A limitation of the entropy measure is that it reflects unpredictability during a very short period of time while the mother completed the relevant questionnaire, rather than unpredictability on a time scale that might be associated with fetal (and brain) development. This limitation is mitigated by the convergent validity results in the new cohort that show an association of the entropy measure with the RMSSD, which is based on affective instability measured over a period of days. A second weakness lies in the fact that this study is necessarily correlational, relying on naturally occurring variations in mood entropy rather than those that are experimentally manipulated. However, our results in humans are consistent with findings from experimental animal models, which demonstrate that exposure to entropy in maternal signals early in development exerts lasting influences on offspring brain and behavior (Brunson et al., 2005; Ivy et al., 2008; Molet et al., 2016).

Existing empirical research indicates that levels of prenatal maternal psychological distress are associated with a range of physical and mental health outcomes. However, interventions to reduce symptoms of anxiety and depression and reduce stress levels during pregnancy have met with only limited success (Fontein-Kuipers et al., 2014). Further, therapeutic strategies focused on increasing clarity and acceptance of emotions seem to be solid targets for positive change (Gratz and Gunderson, 2006; Reinares et al., 2014). Mindfulness-based intervention or interventions targeting alexithymia and emotion regulation are beginning to prove fruitful in treating a range of disorders outside the perinatal period (Kuyken et al., 2016; Spijkerman et al., 2016). It is possible that mood entropy may represent a new target for intervention during the perinatal period, with the potential to augment treatments focused on mood levels or valence. Mental health conditions are likely the downstream consequences of alterations to brain circuits, cognitions and behavior occurring much earlier in life. This new evidence suggests that maternal mood entropy may be a critical predictor of these developmental mental health trajectories and should be considered when assessing early life influences on lifespan mental health.

All authors have seen and approved this manuscript. We confirm that the article is our original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Contributors

All authors contributed to study design and conceptualization. LG, CS and ED were responsible for data collection. LG, MH, HS and MP participated in analyses. LG drafted the manuscript. All authors provided critical editorial feedback.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Figures:

Figure 1. Description of study protocol for Cohorts 1 and 2.
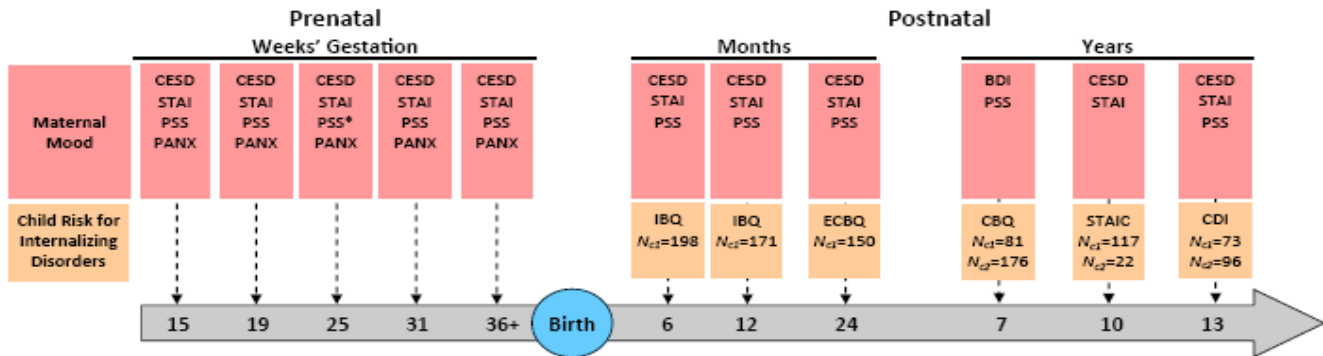
Note: The different numbers of children assessed at each age were determined by the number of children in these longitudinal cohorts who had aged into the assessment window during the NIH-grant periods that funded this work. CESD = Center for Epidemiologic Studies Depression Scale; STAI = State-Trait Personality Inventory; PSS = Perceived Stress Scale; PANX = Pregnancy Specific Anxiety Scale; BDI = Beck Depression Inventory; IBQ = Infant Behavior Questionnaire; ECBQ = Early Childhood Behavior Questionnaire; CBQ = Children's Behavior Questionnaire; STAIC = State-Trait Anxiety Inventory for Children; CDI = Children's Depression Inventory; *PSS not administered at 25 weeks' gestation in Cohort 2

Figure 2. Bivariate correlations between maternal prenatal mood entropy and maternal report of child negative affectivity through 7 years of age (**p < .01).
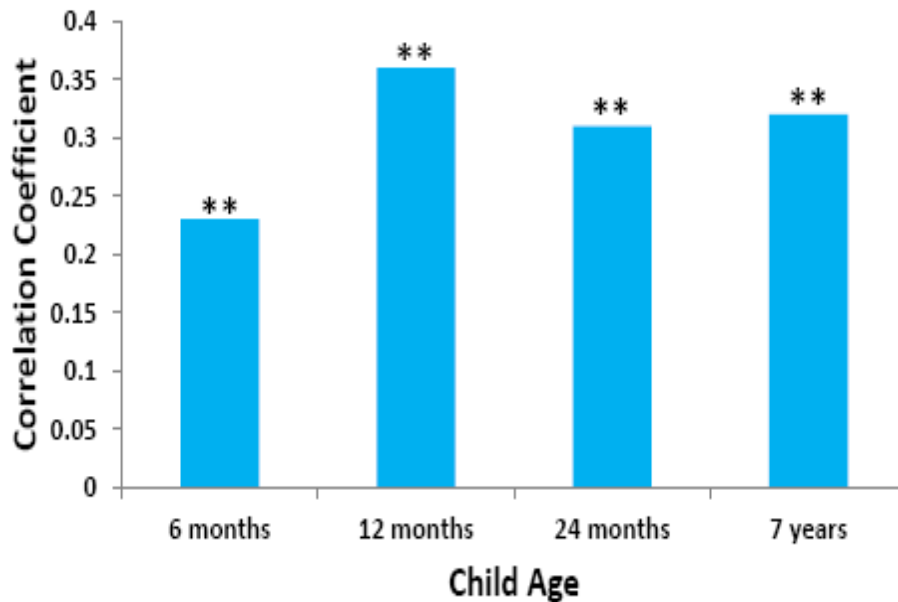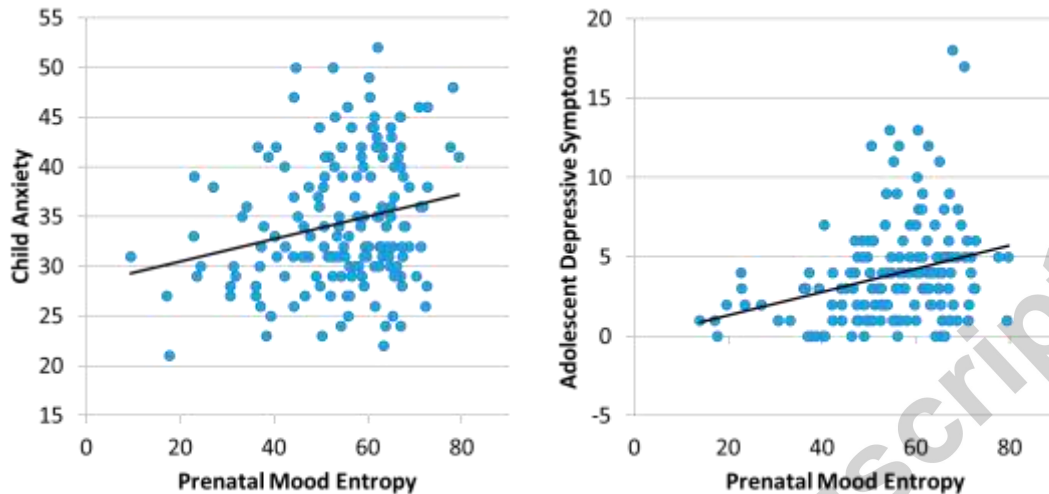
Figure 3. Correlation between maternal prenatal mood entropy and child self-report of anxiety and adolescent self-report of depressive symptoms.

Tables:

Table 1. Participant Characteristics for Cohorts 1 and 2.

	Cohort 1 (N = 227)	Cohort 2 (N = 180)
Maternal Race/Ethnicity (%)		
Latina	27.3	22.0
Black	2.6	10.7
Asian	9.7	11.9
Non-Hispanic White	48.5	50.3
Other	11.9	5.1
Maternal Age (mean years)	30.0	30.8
Education (%)		
High School or Less	14.5	17.0
Some College, Associates or Vocational Degree	40.5	32.2
4-year College Degree	28.6	31.1

Graduate Degree	16.3	19.8
Annual Household Income (mean; US $)	60,784	66,129
Cohabitation with Child's Father (% yes)	89.4	88.0
Birth Order (% first born)	43.6	58.7
Child Sex (% female)	48.5	53.3
Length of Gestation (mean weeks)	39.2	39.0
Mood Entropy (mean)	53.1	57.8

Table 2. Example of Computation of Entropy for STAI (10 items on a 4-point scale)

Item	Response	Coded Response
Calm	1	4
Presently Worrying	2	2
Nervous	2	2
Relaxed	1	4
Worried	2	2
Steady	1	4
Frightened	1	1
Tense	3	3
At Ease	1	4
Jittery	2	2

Response	Frequency	p_e	$p_e \log_2 p_e$
1	1	0.10	-0.33
2	4	0.40	-0.53
3	1	0.10	-0.33
4	4	0.40	-0.53
Sum	10	1.00	-1.72
Normalized Entropy			(1.72/2.00)*100 = 86

Table 3. Summary of regression analyses assessing the contributions of pre and postnatal mood entropy to child outcomes.

	Maternal Report of Negative Affectivity						Child Report of Anxiety and Depressive Symptoms			
	12-mos		24-mos		7-Years		10-years		13-years	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Prenatal Mood Entropy	.25	.00	.21	.02	.23	.00	.17	.06	.24	.00
Postnatal Mood Entropy	.20	.02	.24	.01	.22	.00	.17	.07	.15	.05

Highlights

- Examines prenatal mood unpredictability as a risk factor for child temperament and internalizing symptoms
- Prenatal mood entropy predicts maternal report of child negative affect through 7 years
- Prenatal mood entropy predicts child report of anxiety and 10 and depressive symptoms at 13 years
- Patterns of maternal mood, in addition to level or valence, may influence child development