SUPPLEMENTARY INFORMATION

Prenatal Exposure to Maternal Mood Entropy Is Associated with a Weakened and Inflexible Salience Network in Adolescence

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Eligibility Criteria

The following initial inclusion criteria were used for assessing the eligibility of pregnant woman in this study: English-speaking, adult (18 years old) women with intrauterine, singleton pregnancies. Exclusion criteria were the presence of uterine or cervical abnormalities, conditions such as endocrine, hepatic, or renal disorders or use of corticosteroid medication that could dysregulate neuroendocrine function, and abuse of tobacco, alcohol, or recreational drugs in the pregnancy. Mother–child pairs were included in the current study if the child completed the MRI scanning session during adolescence.

Assessment of Maternal Mood Entropy

Maternal mood was assessed five times during pregnancy at 15, 19, 25, 31 and 36+ gestational weeks. At each prenatal assessment, mothers completed widely-used and validated measures to assess depressive symptoms, state anxiety, pregnancy-specific anxiety, and perceived stress. These mood assessments were repeated concurrent to the child MRI (with the exception of pregnancy-specific anxiety). Entropy scores were computed for each scale using the formula below, where p_i is the proportion of items for which the i-th response choice was made, log_2

indicates the logarithm to the base two, and Σ indicates that the sum is to be taken over all possible response choices.

$$Entropy = \sum_i p_i * log_2(p_i)$$

The entropy values were averaged over the multiple scales for each individual at each time point, and then averaged across time points to provide a single measure for each mother.

Summary of Statistical Equations

Analyses were conducted using the equations listed below, where the response variable was always a derived neuroimaging metric of interest (Integrity or ALFF), except for equation 3. Covariates always included age at scan, sex, and head motion (via the mean framewise displacement). The term, maternal mood, denotes one of the two assessments of prenatal maternal mood (level/entropy) were used within a single model, except in equation 6 were both prenatal mood factors were included in the same model. For analyses conducted across the entire scanning session, a random intercept for each subject was included to account for the fact that each subject contained three observations (1 per MRI scan):

1) $lm(Salience_{Task\ Activation} \sim age + sex + head\ motion + \boldsymbol{maternal\ mood})$

2A) $lmer\left(Salience_{Integrity} \sim age + sex + head\ motion + \boldsymbol{maternal\ mood} + (1 \mid subj)\right)$

2B) $lmer\left(Salience_{Integrity} \sim age + sex + head\ motion + MRI\ scan \times \boldsymbol{maternal\ mood}\right)$

3A) $hlme\big(Salience_{Integrity_\Delta} \sim age + sex + head\ motion + \text{timepoint},$

$$\text{random} = \sim 1 + \text{timepoint}, \quad \text{subject} = \text{subj}, \quad \text{ng} = 1 - 4\big)$$

3B) $t.test(\boldsymbol{maternal\ mood} \sim age + sex + head\ motion + latent\ class\ profiles)$

4) $lmer\big(Salience_{ALFF} \sim age + sex + head\ motion + \boldsymbol{maternal\ mood} + (1 \mid subj)\big)$

5) $lmer\left(Salience_{Metric} \sim age + \ head\ motion + sex \times \boldsymbol{maternal\ mood} \ + \ (1 \mid subj)\right)$

6) $lmer\left(Salience_{Metric} \sim age + \ sex + head\ motion + \ \boldsymbol{mood_{level}} + \ \boldsymbol{mood_{entropy}}\ (1 \mid subj)\right)$

Sensitivity Analyses Accounting for the Confounding Influences of Head Motion

To further assess the strength of the relationships with mood entropy, the original models were re-run while excluding 77 high motion scans out of the 414 scans available (mean framewise displacement > 0.50 mm). Analyses with this subset of participants confirmed the original results; mood entropy remained associated with salience integrity (β=-0.42, t=-2.15, p=0.03) and ALFF (β=-0.27, t=-3.04, p<0.01).

Sensitivity Analyses Accounting for Socioeconomic Status

To ensure that our findings were not driven by socioeconomic status, we performed sensitivity analyses using income-to-needs ratio (INR) in the models (mean: 579; standard deviation: 750; range: 75 - 5752). INR was determined by comparing household income to the federal poverty line for a given year, which also scaled with household size (1,2). A ratio below one indicates that a given household is below the federal poverty line. Given that our sample contained a few participants from high-income families, we log-transformed INR to obtain a more normal distribution. When controlling for log-transformed INR, the association between prenatal mood entropy and salience network ALFF remained statistically significant (β=-0.22, t=-2.57, p=0.01) but salience network integration become only marginally associated (β=-0.10, t=-1.87, p=0.06). Prenatal maternal mood level remained unassociated with the integrity of the salience network (β=-0.04, t=-0.73, p=0.46), and its relation with salience network ALFF persisted (β=-0.18, t=-2.05, p=0.04). There was a slight trend in INR differences between our two latent profiles that displayed distinct patterns of network integration throughout the MRI scanning session (d=1.72; t=1.69; p=0.09).

Properties of the Salience Network does not Mediate Relations between Prenatal Mood and Depressive Symptoms.

Prior research has demonstrated that depressive symptoms in adolescents is associated with exposure to both prenatal maternal mood level ($\beta=0.16$, $t=3.32$, $p<0.001$) and entropy ($\beta=-0.18$, $t=3.67$, $p<0.001$) (3). Here, we sought to further understand whether these relationships were mediated by individual differences in the integrity or ALFF of the salience network. As such, we quantified depressive symptoms using the Center for Epidemiological Studies Depression Scale (4), which was collected at the time of MRI scanning. We did not detect any mediation effects, whereby the relationship between prenatal mood entropy and depressive symptoms did not weaken when covarying for salience network integrity ($\beta=-0.19$, $t=3.86$, $p<0.001$) or ALFF ($\beta=-0.18$, $t=3.54$, $p<0.001$). Similarly, the relation between prenatal mood level and depressive symptoms remained the same when covarying for salience network ALFF ($\beta=0.16$, $t=3.21$, $p<0.001$) and strengthened when covarying for salience network integrity ($\beta=0.17$, $t=3.41$, $p<0.001$). These results suggest that the relation between prenatal mood and depressive symptoms are not likely explained by neurodevelopmental differences in the salience network.

SUPPLEMENTARY REFERENCES

1. Grieger LD, Danziger S, Schoeni RF (2009): Accurately measuring the trend in poverty in the United States using the Panel Study of Income Dynamics. *Journal of Economic and Social Measurement* 34: 105–117.
2. Granger SJ, Glynn LM, Sandman CA, Small SL, Obenaus A, Keator DB, *et al.* (2021): Aberrant maturation of the uncinate fasciculus follows exposure to unpredictable patterns of maternal signals. *Journal of Neuroscience* 41: 1242–1250.
3. Glynn LM, Howland MA, Sandman CA, Davis EP, Phelan M, Baram TZ, Stern HS (2018): Prenatal maternal mood patterns predict child temperament and adolescent mental health. *Journal of Affective Disorders* 228: 83–90.
4. Santor DA, Coyne JC (1997): Shortening the CES–D to improve its ability to detect cases of depression. *Psychological assessment* 9: 233.

Table S1. Latent growth curve modeling of salience integrity yielded a two-profile solution.

Classes	Log Likelihood	BIC	AIC	Entropy	Class-1	Class-2	Class-3	Class-4
1	-1144.13	2233	2306	1.000	100 %	-	-	-
2	**-1038.65**	**2161**	**2111**	**0.772**	**37.0 %**	**63.0 %**	**-**	**-**
3	-1038.65	2200	2127	0.856	37.0 %	0 %	63.0 %	-
4	-1021.50	2205	2109	0.792	2.9 %	42.8 %	31.2 %	23.2 %

Note. The resulting 2 class solution was used for subsequent analyses, as it contained the lowest Bayesian information criterion (BIC) and Akaike information criterion (AIC) while also having a relatively equal number of participants across clusters. Although the 4-class model contained a smaller AIC, both models with 3 or 4 classes did not converge. Bold font denotes the 2-class model that was selected for analyses in this study.

Table S2. Relationships between prenatal mood exposure and properties of the salience network were not moderated by sex differences.

Variable of Interest	Mood Level	Mood Entropy
Salience Integrity	β = 0.02, t = 0.34, p = 0.73	β= 0.02, t = 0.40, p = 0.69
Salience ALFF	β = 0.09, t = 1.15, p = 0.25	β= 0.14, t = 1.75, p = 0.08

Note. The interaction terms reported above were yielded from an mixed effect model: $lmer\big(Salience_{Metric} \sim age + \ head\ motion + (\boldsymbol{sex} \times \boldsymbol{prenatal\ adversity}) + (1 \mid subj)\big)$. For interpretability, males obtained a dummy score of 1 and females were encoded with a value of 0. These results suggest that males and females had similar relationships between prenatal maternal mood entropy and proprieties of the salience network, thereby such results were not driven by potential sex-differences.

Table S3. Mixed effect models suggested that mood entropy remained associated with salience integrity when accounting for exposure to negative maternal mood level.

Variable of Interest	Salience Integrity	Salience ALFF
Age at Scan	β = -0.05, t = -1.00, p = 0.31	β = -0.12, t = -1.47, p = 0.14
Sex	β = 0.08, t = 1.52, p = 0.13	β = 0.08, t = -1.04, p = 0.29
Head Motion	β = -0.06, t = -1.16, p = 0.27	**β = 0.09, t = 2.44, p = 0.01**
Mood Level	β = 0.07, t = 0.85, p = 0.41	β = -0.03, t = -0.21, p = 0.83
Mood Entropy	**β = -0.16, t = -2.00, p = 0.04**	β = -0.17, t = -1.43, p = 0.15

Note. Each row reports the t-value and p-value for each predictor within a given model. Each column corresponds to a different model with column 1 predicting salience integrity and column 2 predicting the ALFF in the salience network.

Table S4. Mixed effect models suggested that the relationships between the salience network and prenatal maternal mood entropy were mostly consistent when controlling for current maternal mood entropy.

Variable of Interest	Salience Integrity	Salience ALFF
Age at Scan	β = -0.06, t = -1.05, p = 0.29	β = -0.12, t = -1.45, p = 0.15
Sex	β = 0.16, t = 1.55, p = 0.12	β = 0.16, t = -1.03, p = 0.30
Head Motion	β = -0.05, t = -0.98, p = 0.33	**β = 0.08, t = 2.42, p = 0.02**
Prenatal Mood Entropy	β = 0.10, t = 1.77, p = 0.08	**β = -0.20, t = -2.37, p = 0.02**
Postnatal Mood Entropy	β = -0.02, t = -0.36, p = 0.72	β = 0.03, t = 0.35, p = 0.73

Note. Each row reports the t-value and p-value for each predictor within a given model. Each column corresponds to a different model with column 1 predicting salience integrity and column 2 predicting the ALFF in the salience network.

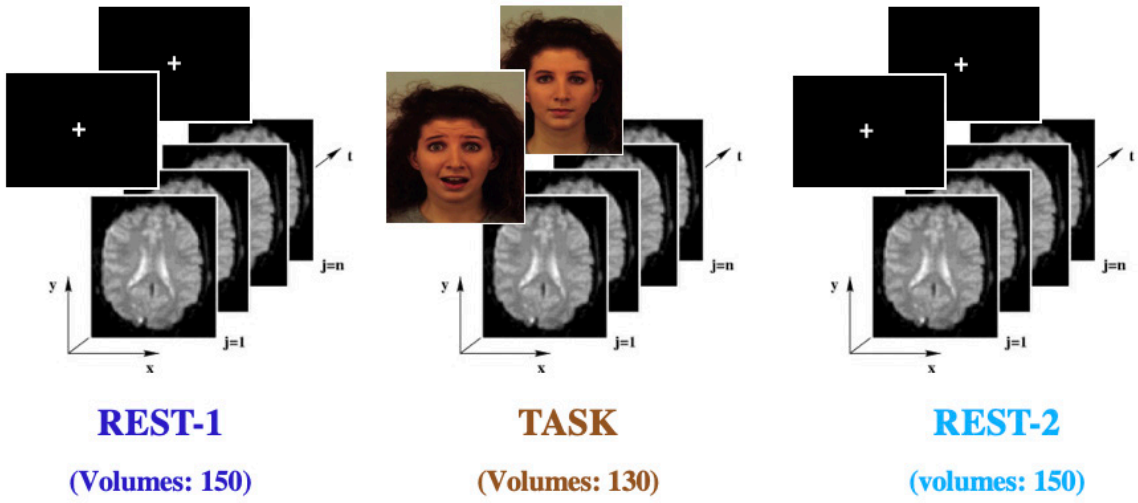

Figure S1. **fMRI Study Design and Procedure.** Two resting-state fMRI scans were acquired in between a task-based fMRI scan. Participants were instructed to keep their eyes fixed on a crosshair in the center of the screen for the resting-state scans. During the task-based scan, participants passively viewed faces with either neutral or fearful expressions. A total of 430 volumes were acquired across all three fMRI scans for each participant.

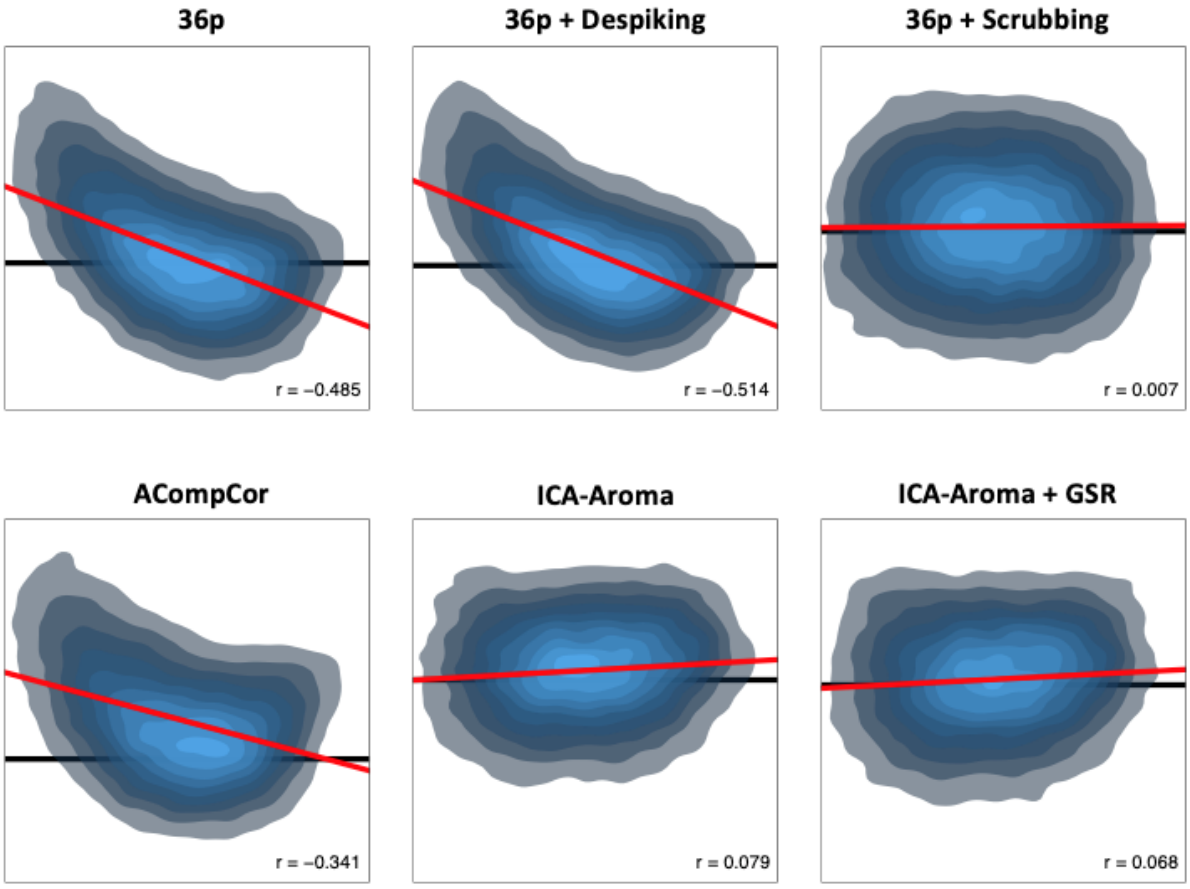

Figure S2. **All fMRI scans were processed through multiple denoising pipelines to evaluate which methods were best at attenuating distance-dependent artifacts.** Given the high amounts of head motion, a robust quality assurance analysis was performed to find the most efficient fMRI denoising method. Aligning with prior benchmarks from the XCP-Engine, we found that the ICA-AROMA pipeline was superior at mitigating motion confounds while preserving the most temporal degrees of freedom. Motion is known to increase the connectivity nearby nodes while simulations reducing connectivity of nodes that are further away. We did not find this negative relationship in our data, as the ICA-AROMA yielded a minor positive correlation between functional connectivity and the Euclidean distance between nodes.

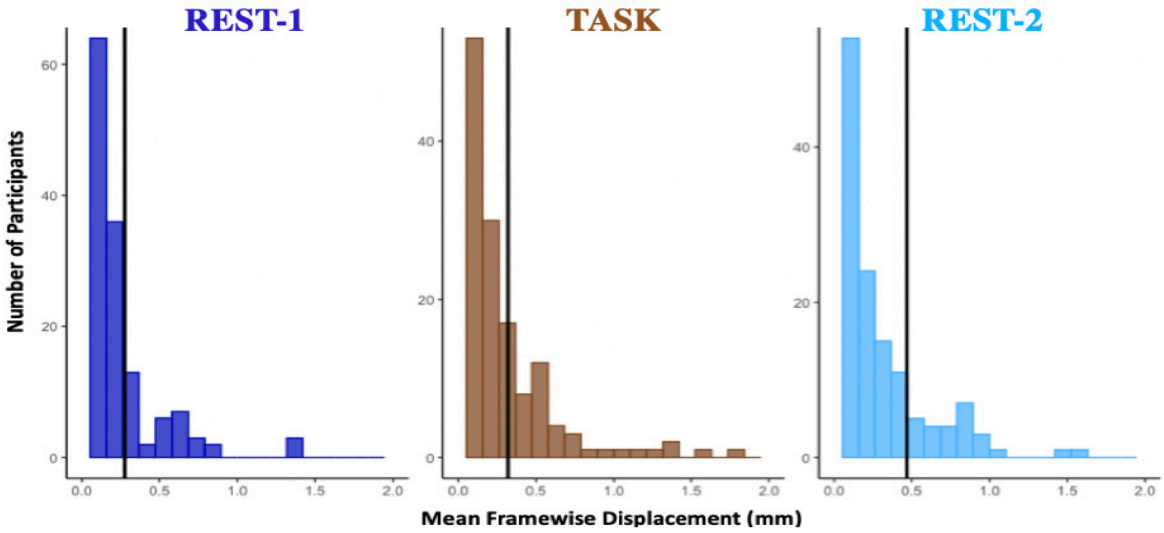

Figure S3. **Head motion increased with each successive fMRI scan.** This can be observed as the average head motion across all participants was 0.27 mm during the baseline resting scan, 0.32 mm during the task, and 0.47 during the follow-up resting-state scan. The black vertical lines denote the group means for each of the three fMRI scans.

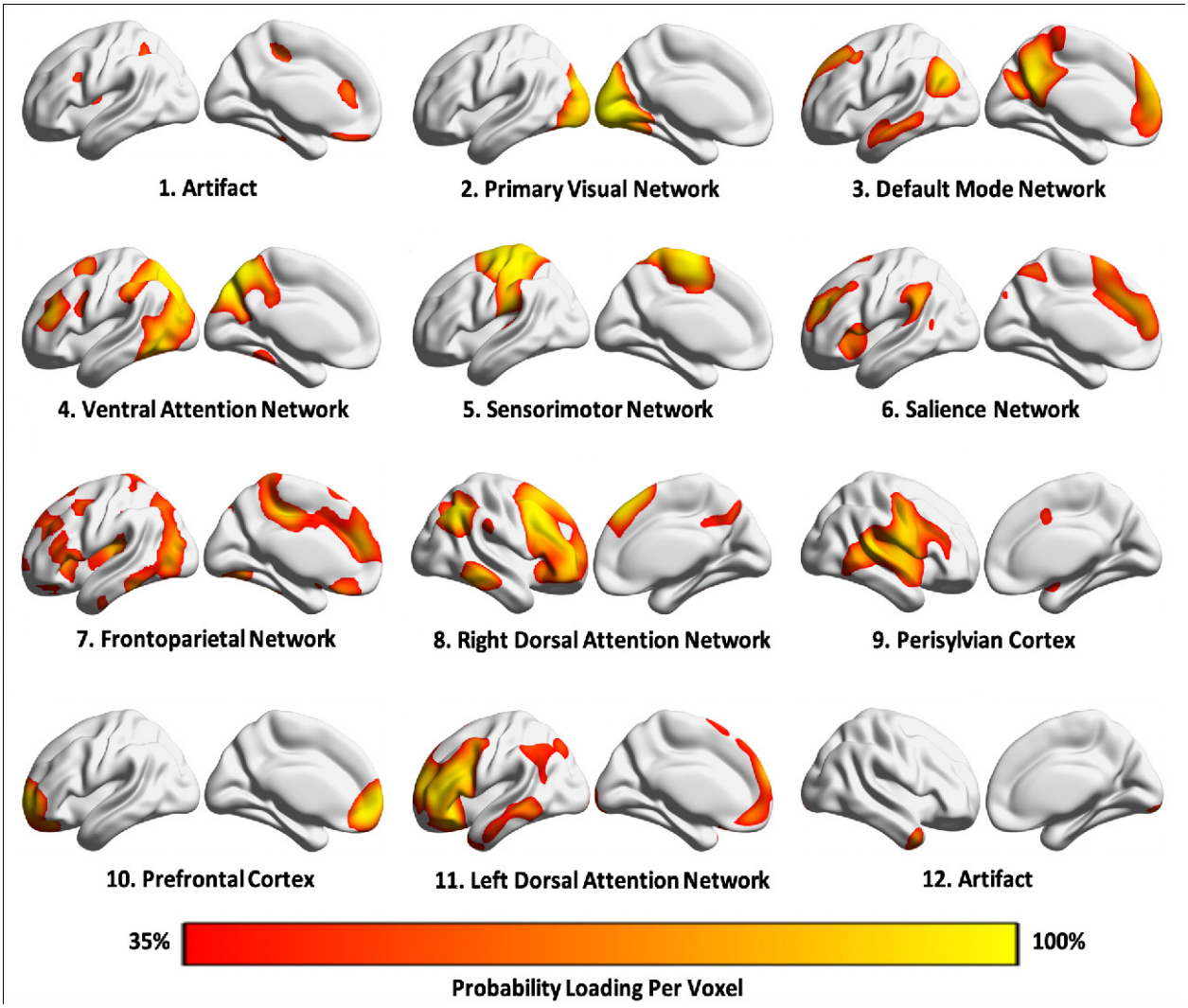

Figure S4. Parcellations of intrinsic connectivity networks. Visualization of the 12 functional covariance networks derived by group independent component analysis. For visualization purposes, each brain map was smoothed by a 6 mm kernel and a threshold was applied to retain only the voxels that had greater than a 35% probability of mapping onto a given component. Intrinsic connectivity networks were identified by visual inspection. All components were bilaterally distributed, except for the left (#8) and right (#11) dorsal attention network.

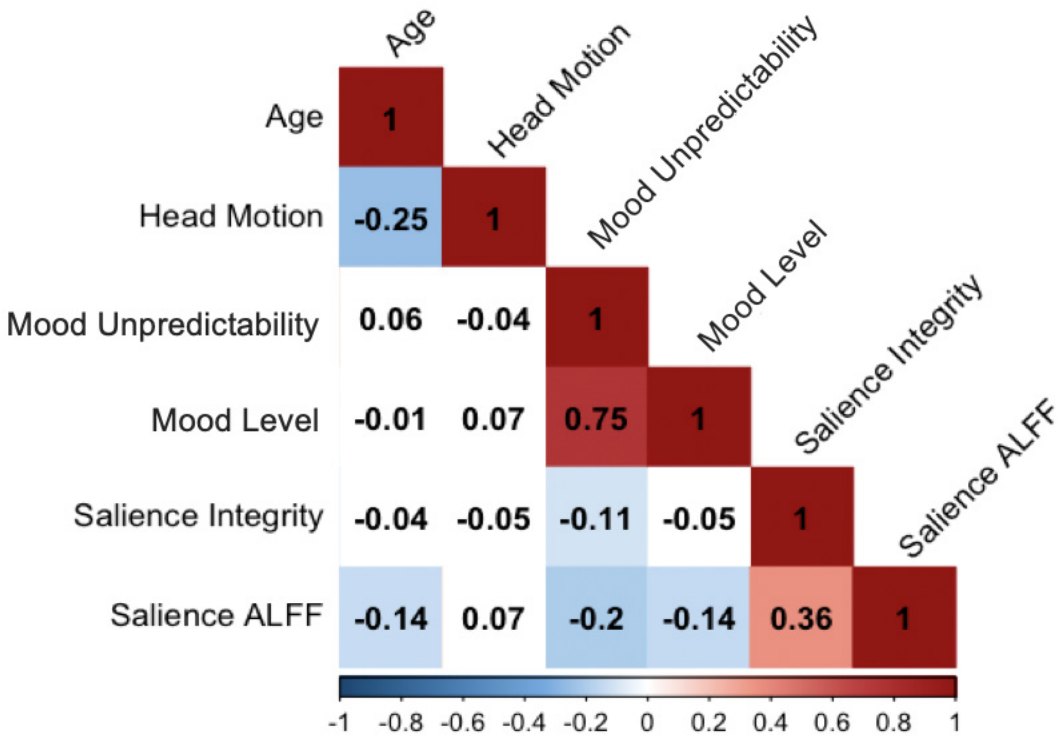

Figure S5. **Matrix showing the pairwise correlations of all numerical variables of interest in this study.** The boxes are color coded to indicate whether a given pairwise correlation was significant at an uncorrected threshold, with red denoting positive associations and blue representing negative relationships. Measures of head motion, salience integrity, and salience ALFF were averaged across the three scans for each participant. Prenatal maternal mood entropy displayed stronger correlations with properties of the salience network relative to mood level.

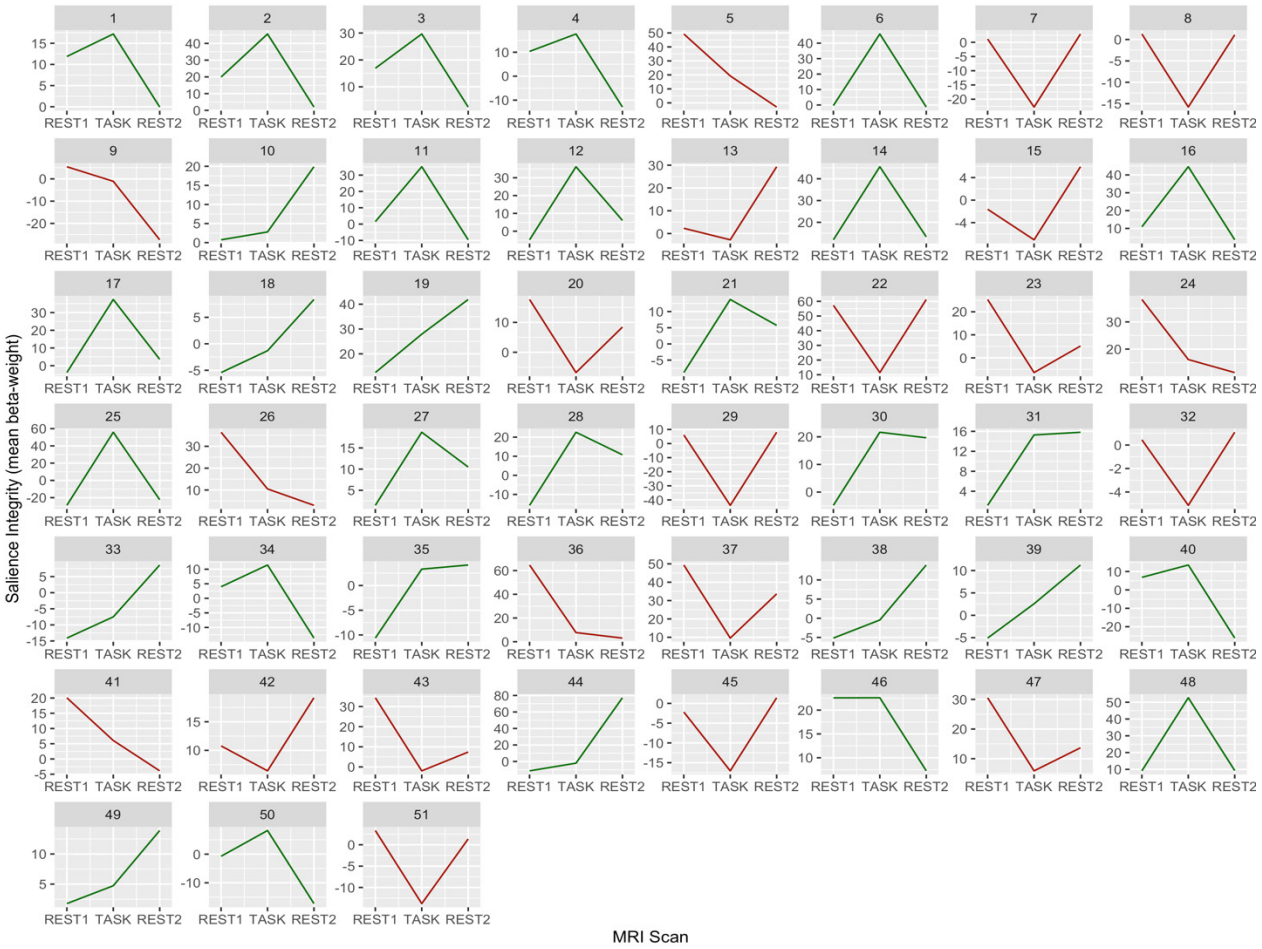

Figure S6. **Differences between participants in the variable cluster were negligible.** The variable cluster contained participants whose activation either increased (n = 30; shaded in green) or decreased (n = 21; shaded in red) when engaging in the task-based MRI scan. We further explored whether these two subgroups differed along a variable of interest. However, we did not detect any significant differences in terms of age (t= 1.35; p= 0.18), gender (X^2 = 1.34; p= 0.25), head motion (t= 0.74; p= 0.46), prenatal mood level (t= 0.83; p= 0.41), or prenatal mood entropy (t= 0.24; p= 0.81). Numerical variables were analyzed using the Welch two sample t-test, whereas sex-differences were assessed using a chi-squared test.