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# Persistence, Reward Dependence, and Sensitivity to Reward Are Associated With Unexpected Salience Response in Girls but Not in Adult Women: Implications for Psychiatric Vulnerabilities

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## ABSTRACT

**BACKGROUND:** Adolescence is a critical period for the development of not only personality but also psychopathology. These processes may be specific to sex, and brain reward circuits may have a role. Here, we studied how reward processing and temperament associations differ across adolescent and adult females.

**METHODS:** A total of 29 adolescent girls and 41 adult women completed temperament assessments and performed a classical taste conditioning paradigm during brain imaging. Data were analyzed for the dopamine-related prediction error response. In addition, unexpected stimulus receipt or omission and expected receipt response were also analyzed. Heat maps identified cortical-subcortical brain response associations.

**RESULTS:** Adolescents showed stronger prediction error and unexpected receipt and omission responses (partial $\eta^2$ = 0.063 to 0.166; $p$ = .001 to .043) in insula, orbitofrontal cortex (OFC), and striatum than adults. Expected stimulus receipt response was similar between groups. In adolescents versus adults, persistence was more strongly positively related to prediction error (OFC, insula, striatum; Fisher's $z$ = 1.704 to 3.008; $p$ = .001 to .044) and unexpected stimulus receipt (OFC, insula; Fisher's $z$ = 1.843 to 2.051; $p$ = .014 to .033) and negatively with omission (OFC, insula, striatum; Fisher's $z$ = −1.905 to −3.069; $p$ = .001 to .028). Reward sensitivity and reward dependence correlated more positively with unexpected stimulus receipt and more negatively with stimulus omission response in adolescents. Adolescents showed significant correlations between the striatum and FC for unexpected stimulus receipt and omission that correlated with persistence but were absent in adults.

**CONCLUSIONS:** Associations between temperamental traits and brain reward response may provide neurotypical markers that contribute to developing adaptive or maladaptive behavior patterns when transitioning from adolescence to adulthood.


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Adolescence is a developmentally critical period for temperamental traits to interact with the environment and establish character and personality (1,2). Adolescence is also a time of ongoing maturation of neurotransmitter systems, which can create neurobiological vulnerabilities for developing psychiatric disorders (3–5). In fact, about half of all psychiatric disorders manifest by age 14 years, and three fourths by 24 years (6). Temperamental traits for emotion expression and reward sensitivity are thought to play a role (7–9).

These observations have raised the question of whether age- and sex-specific neurobiological markers can be identified that could indicate vulnerabilities for developing psychopathology (10). The contribution of cortical and subcortical activation to the motivational system and related reward circuitry changes during development and could be a key target to study such vulnerabilities (11). Consistent with that hypothesis is that the brain prediction error response, a dopamine-related neuronal brain response to unexpected receipt or omission of salient stimuli, was elevated in adolescents compared with adults (12). The prediction error model is of particular interest because it is well understood and important for adaptive learning (13). Another study on reward processing in adolescents but without an adult comparison group found reward response in adolescents related to sensation seeking (14). Clinical samples indicated lower brain reward response in adolescents with higher levels of depression, while prediction error reward response was elevated in adolescents with anorexia nervosa and high anxiety (15,16).

How temperamental traits relate to the developing reward circuitry and differentiate adolescents from adults has not been well studied. Understanding this relationship is important because temperamental traits could be directly related to or

 

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drive neuronal reward response and could either facilitate development of functional behavior patterns including emotion regulation learning or lead to excessive frustration, anxiety, or mood disturbance if the reward system cannot flexibly adapt when, for instance, reward expectations are not met (17,18).

This study had several goals. First, we wanted to test whether we would find elevated taste reward prediction error response using a computational analysis approach in adolescents compared with adults in regions that separated healthy adolescents from a psychiatrically ill group previously (12,16). While a recent large dataset indicated similar brain reward responses for girls and boys, sex differences have been identified with respect to psychopathology, and we contrasted girls and young women for this study (10,14). To separately assess expected or unexpected receipt and omission response, without including a value component, we added a group-by-condition analysis (19). Because emotion regulation and response to nonreward are developmental challenges in adolescents, we expected that stimulus omission would especially distinguish age groups (20). We also analyzed expected stimulus receipt as a control condition, not expecting group differences.

Second, we wanted to test differences in associations between brain response and temperament across age groups. Prediction error response is relatively stable in adolescents but differs from that in adults, while temperamental traits are comparable across age groups (12,14,21,22). We hypothesized that the reward-responsive traits novelty seeking, persistence, and sensitivity to reward would be positively correlated with prediction error response as a sign of impulsive, reward-oriented behavior in adolescents but not in adults (23). Those traits derived, in part, from Cloninger's Temperament and Character Inventory, "quantify individual differences in associative conditioning," suggesting adaptation of the neuronal response in the transition from adolescence to adulthood, based on life experience and conditioning (24–27). Taste perception could be a trait that contributes to reward response, and sweetness and pleasantness were assessed across age groups as well (28).

Third, we wanted to test whether the number of cortical regions or networks that the subcortical reward response recruits (clusters or associated brain response) differ across age groups. If specific subcortical brain responses were to be stronger related to frontal cortex activation in adolescents, this could further indicate the particular importance of reward-related response for learning in that age group.

## METHODS AND MATERIALS

### Study Participants

The Colorado Multiple Institutional Review Board approved the study. All participants gave written informed consent before study procedures commenced. We recruited from the community 29 healthy adolescent girls and 41 healthy young adult women (Table 1). Participants were studied during the early follicular phase to control sex hormone effects. To rule out psychopathology, participants 18 years or older were administered the Structured Clinical Interview for DSM-5 (by a doctoral-level clinician). Those younger than 18 years completed the Mini-International Neuropsychiatric Interview (29). Participants were right-handed without history of head trauma, neurological disease, major medical illness, or psychiatric disorder. Participants completed the Temperament and Character Inventory (30) and the Revised Sensitivity to Punishment and Reward Questionnaire (31). Subjects rated sucrose solutions and artificial saliva (3 mM KCl, 0.25 mM $NaHCO_3$) (32) for sweetness and pleasantness using a 9-point Likert Scale (Supplement). A 1 molar sucrose solution was used in the functional magnetic resonance imaging (fMRI) paradigm.

### Brain Imaging Methods

**fMRI Image Acquisition.** Between 7:00 AM and 9:00 AM, participants ate a standard breakfast. Brain imaging was performed between 8:00 AM and 9:00 AM on a 3T GE Signa scanner (GE Healthcare, Waukesha, WI) (three-plane scout scan 16 s) for sagittally acquired, spoiled gradient sequence T1-weighted, 172 slices, thickness = 1 mm, inversion time = 450 ms, repetition time = 8 ms, echo time = 4 ms, flip angle = 12°, field of view = 22 cm, scan matrix = 64 × 64, and T2*-

**Table 1. Demographic and Behavioral Data Across Groups**

| | Adolescents | | Adults | | 95% CI | | | |
|---|---|---|---|---|---|---|---|---|
| Demographics | Mean | SD | Mean | SD | Lower | Upper | *t* | *p* Value |
| Age, Years | 15.155 | 1.916 | 26.527 | 5.425 | −13.473 | −9.272 | −10.804 | <.001 |
| Body Mass Index, kg/m$^2$ | 21.236 | 1.915 | 21.600 | 1.442 | −1.165 | 0.436 | −0.908 | .367 |
| Novelty Seeking | 21.410 | 5.742 | 18.100 | 4.800 | 0.794 | 5.838 | 2.624 | .011 |
| Harm Avoidance | 10.690 | 5.670 | 11.270 | 5.563 | −3.294 | 2.136 | −0.425 | .672 |
| Reward Dependence | 15.520 | 4.006 | 16.760 | 3.506 | −3.040 | 0.562 | −1.373 | .174 |
| Persistence | 5.100 | 1.319 | 5.490 | 1.287 | −1.014 | 0.245 | −1.218 | .227 |
| Intolerance of Uncertainty | 46.930 | 12.262 | 51.850 | 12.972 | −11.064 | 1.219 | −1.599 | .114 |
| Trait Anxiety | 29.210 | 6.795 | 28.070 | 5.867 | −1.900 | 4.167 | 0.746 | .458 |
| Reward Sensitivity | 6.410 | 4.005 | 4.850 | 3.198 | −0.937 | 3.077 | 1.064 | .291 |
| Punishment Sensitivity | 4.970 | 3.407 | 4.630 | 2.709 | −1.643 | 2.027 | 0.209 | .835 |
| Pleasantness 1 Molar Sucrose | 5.070 | 2.477 | 5.340 | 2.220 | −1.400 | 0.856 | −0.482 | .631 |
| Sweetness 1 Molar Sucrose | 8.280 | 0.996 | 8.050 | 0.805 | −0.203 | 0.657 | 1.053 | .296 |

weighted echo-planar scans for blood oxygen level–dependent functional activity (3.4 × 3.4 × 2.6 mm voxels, repetition time = 2100 ms, echo time = 30 ms, flip angle = 70°, 28 axial slices, thickness = 2.6 mm, gap = 1.4 mm).

**Taste Reward Task.** Participants learned to associate three unconditioned taste stimuli (unconditioned stimulus [US]: 1M sucrose solution, no solution, or artificial saliva) with paired conditioned visual stimuli (conditioned stimulus [CS]) (32) (Supplement). Each CS was probabilistically associated with its US such that 20% of sucrose and no-solution CS trials were unexpectedly followed by no-solution and sucrose US, respectively. Taste stimuli were applied using a customized programmable syringe pump (J-Kem Scientific, St Louis, MO) and E-Prime Software (PST, Pittsburgh, PA) (33).

**fMRI Data Preprocessing.** Image preprocessing and analysis were performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Images were realigned to the first volume, normalized to the Montreal Neurological Institute template, and smoothed at 6-mm full width at half maximum Gaussian kernel. Data were preprocessed with slice time correction and modeled with a hemodynamic response convolved function using the general linear model, including temporal and dispersion derivatives. A 128-second high-pass filter for low-frequency blood oxygen level–dependent signal fluctuations and motion parameters as first-level analysis regressors were applied.

**Prediction Error Analysis.** Each participant's prediction error signal was modeled based on trial sequence and regressed with brain activation across all trials (32,34,35). The predicted value ($\widehat{V}$) at any time ($t$) within a trial is calculated as a linear product of weights ($w_i$) and the presence of a visual CS at time $t$, coded in a stimulus representation vector $x_i(t)$ where each stimulus $x_i$ is represented separately at each moment in time:

$$V(t) = \sum_i W_i x_i(t)$$

Predicted stimulus value at time $t$ is updated by comparing the predicted value at time $t+1$ to that actually observed at time $t$, leading to the prediction error $\delta(t)$:

$$\delta(t) = r(t) + \gamma \widehat{V}(t+1) - \widehat{V}(t)$$

where $r(t)$ is the reward at time $t$. The parameter $\gamma$ is a discount factor, which determines the extent to which rewards arriving sooner are more important than rewards that arrive later during the task, with $\gamma = 0.99$. The weights $w_i$ relate to how likely a particular reward US follows the associated CS and are updated on each trial according to the correlation between prediction error and the stimulus representation:

$$\Delta w_i = \alpha \sum_t x_i(t)\delta(t)$$

where $\alpha$ is a learning rate. A slow $\alpha = 0.2$ was applied (see the Supplement). Initial reward values were 1 for sucrose receipt and 0 for no sucrose. Trial-to-trial prediction error was regressed with brain activation across all trials within each subject. The prediction error calculated for each trial was modeled as an absolute (reflecting degree of deviation of the outcome from the expectation) without separating positive or negative prediction error trials. Model prediction error values were then regressed against the fMRI data for each individual subject to identify brain regions correlating with the model-predicted time series (36).

**Group-by-Condition Analysis.** We developed first-level models to predict the response in each voxel as a function of each of five stimulus conditions: expected sucrose, unexpected sucrose, expected no solution, unexpected no solution, and expected artificial saliva. Three contrasts of interest were computed per subject: 1) unexpected sucrose receipt: trials with CS for no solution followed by unexpected US sucrose contrasted against trials with CS for no solution followed by expected no solution; 2) unexpected sucrose omission: trials with CS for sucrose solution followed by unexpected US no solution contrasted against trials with CS for sucrose solution followed by expected sucrose solution; and 3) expected sucrose receipt: trials with CS for sucrose solution followed by expected US sucrose contrasted against trials with CS for artificial saliva solution followed by expected US artificial saliva.

**Region of Interest Data Extraction.** We extracted parameter estimates (prediction error analysis) and beta values (group-by-condition analyses) from predefined regions of interest (ROIs) bilaterally (http://marsbar.sourceforge.net/, automated anatomical labeling atlas) (37): superior, middle, medial, and inferior orbitofrontal cortex (OFC); dorsal anterior insula, ventral anterior insula, posterior insula; caudate head; putamen; and ventral striatum (38) and nucleus accumbens (39).

**Associated Brain Region Analysis.** We calculated within-group ROI correlations and imported those correlation $p$ values into Tableau software (www.tableau.com). For this analysis, we added bilateral superior, superior medial, and middle FC; anterior, middle, and posterior cingulate cortex (CC); and substantia nigra to test association with regions that are tasked with higher-order cognitive and emotional processing for a total of 36 brain regions bilaterally.

## Statistical Analysis

SPSS 26 software (IBM Corp., Armonk, NY) was used for statistical analyses. All data were tested for normality with the Shapiro-Wilk test and rank transformed and normalized (Rankit formula) when non-normally distributed. Demographics and extracted regional brain response group comparisons were analyzed using Student's $t$ test. Pearson correlation coefficient was used to test for significant correlations within groups.

Age and body mass index (in kg/m$^2$) can affect reward processing response, and partial correlations adjusted for those variables in the within-group analyses for behavior-brain correlations. To compare groups for correlation slopes, the Fisher $z$-transformation was applied. Group contrasts and brain-behavior correlations were controlled for multiple

comparisons using false discovery rate (40) and bootstrapping (1000 samples) (41).

For within-group–related brain response cluster maps, we calculated correlations for activation strength between ROIs. ROI correlations were corrected using the Bonferroni method for 5184 comparisons per group (36 × 36 ROI correlations and four conditions, setting the $p$ value threshold at $p < .000009$). Results were thresholded and presented in Tableau software.

## RESULTS

### Demographic Data

Demographic data were matched between groups except for age (Table 1). Twenty-four adolescents were Caucasian, 4 were African American, and 1 belonged to more than one race; 37 adults were Caucasian, 2 were African American, and 2 belonged to more than one race ($\chi^2_3 = 3.035$, $p = .386$). Adolescents had 10.2 ± 2.7 years and adults 16.2 ± 2.4 years of education. Age and body mass index were not significantly correlated in either group but were significantly correlated with multiple regional brain imaging data and were controlled for in the within-group correlation analyses.

### Taste Reward Processing, Group Contrasts

Both groups showed the expected positive brain activation to unexpected receipt but negative brain response to unexpected stimulus omission beta values (Figure S2 and Table 2).

A mixed multivariate analysis of variance (two groups, four conditions, 22 brain regions) indicated a significant group × condition interaction: Wilks' $\lambda = 0.819$, $F_{36} = 4.862$, $p = .004$, partial $\eta^2 = 0.181$ (large effect size). Post hoc analyses showed the group contrasts below.

**Prediction Error Regression.** Adolescents showed significantly higher regression with the computational model data than adults in bilateral middle and inferior OFC, bilateral dorsal anterior, left ventral anterior, and bilateral posterior insula.

**Unexpected Sucrose Receipt.** Adolescents showed a stronger, more positive response in right superior, bilateral middle, left medial, and bilateral inferior OFC; bilateral dorsal anterior insula; and bilateral caudate head, putamen, and ventral striatum.

**Unexpected Sucrose Omission.** Adolescents showed stronger, more negative responses in almost all regions tested, except for the left superior and bilateral medial OFC, bilateral caudate head, and nucleus accumbens.

**Expected Sucrose Receipt.** No significant group differences were found.

### Taste Reward Processing, Correlation Analyses Group Contrasts

**Prediction Error Regression.** In adolescents, persistence correlated positively with response in left superior and inferior OFC, left dorsal and ventral anterior insula, posterior insula, caudate head, and ventral striatum (Table 3). In adults, harm avoidance correlated negatively with response in right superior OFC (Table S1). Adolescents versus adults differed for persistence and left superior OFC, inferior OFC, dorsal anterior insula, ventral anterior insula, posterior insula, bilateral caudate head, left putamen, and nucleus accumbens; harm avoidance and right superior OFC (Table S1).

**Unexpected Sucrose Receipt.** In adolescents, reward dependence correlated positively with brain response in bilateral superior OFC, left inferior OFC, and dorsal and ventral anterior insula. Persistence correlated positively with left superior and middle OFC, bilateral inferior OFC, and left dorsal anterior, ventral anterior, and posterior insula. No significant correlations were found in adults. Adolescents and adults differed in reward dependence and bilateral superior OFC, persistence and left middle and bilateral inferior OFC and left dorsal anterior and ventral anterior insula (Table 3).

**Unexpected Sucrose Omission.** In adolescents, reward dependence correlated negatively with left middle and bilateral inferior OFC, left dorsal and ventral anterior insula, bilateral caudate head, right putamen, bilateral ventral striatum, and right nucleus accumbens. Persistence correlated significantly negatively bilaterally with all orbitofrontal, insular, and subcortical regions. Reward sensitivity correlated significantly negatively with bilateral inferior OFC; left dorsal anterior, right ventral anterior, and left posterior insula; bilateral caudate head; and left putamen. No significant correlations were found in adults. Adolescents and adults differed in reward dependence and right inferior OFC, right dorsal and ventral anterior insula, bilateral caudate head, right putamen, and ventral striatum; persistence and all orbitofrontal regions, bilateral dorsal anterior, right ventral anterior and left posterior insula, and all striatal regions; reward sensitivity and bilateral inferior OFC, left posterior insula, bilateral caudate head, and left putamen (Table 3).

**Expected Sucrose Receipt.** In adolescents, taste pleasantness correlated negatively with response in left superior OFC, left ventral anterior insula, bilateral putamen, ventral striatum, and left nucleus accumbens. Sweetness perception correlated significantly negatively with bilateral middle and inferior OFC and bilateral dorsal anterior insula. In adults, taste pleasantness correlated negatively with response in bilateral superior inferior OFC, right dorsal anterior insula, bilateral ventral anterior insula, right putamen, and bilateral ventral striatum. Adolescents versus adults differed for sweetness perception and bilateral middle (right: $z = -2.877$, $p = .002$; left: $z = -2.489$, $p = .006$) and inferior OFC (right: $z = -2.908$, $p = .002$; left: $z = -2.972$, $p = .001$), bilateral dorsal anterior (right: $z = -3.301$, $p < .001$; left: $z = -2.77$, $p = .003$) and ventral insula (right: $z = -2.385$, $p = .009$; left: $z = -2.676$, $p = .005$), and bilateral putamen (right: $z = -3.049$, $p = .001$; left: $z = -2.775$, $p = .003$) (Table S4).

### Brain Network Analysis for Associated ROI Activation

**Prediction Error.** Both groups showed clusters of significant correlations within anatomically related ROIs, between

**Table 2. Reward Response Group Differences**

| | Adolescents | | Adults | | 95% CI | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SE | Mean | SE | Lower | Upper | ES (Partial $\eta^2$) | Power | *t* | *p* Value |
| Prediction Error Response | | | | | | | | | | |
| Superior OFC R | 0.292 | 0.202 | −0.206 | 0.135 | 0.027 | 0.995 | 0.063 | 0.558 | 2.136 | .040[a] |
| Superior OFC L | 0.129 | 0.203 | −0.091 | 0.141 | −0.246 | 0.660 | 0.012 | 0.148 | 0.917 | .347 |
| Middle OFC R | 0.391 | 0.191 | −0.277 | 0.135 | 0.191 | 1.101 | 0.113 | 0.827 | 2.944 | .006[a] |
| Middle OFC L | 0.366 | 0.202 | −0.259 | 0.129 | 0.175 | 1.062 | 0.099 | 0.768 | 2.730 | .014[a] |
| Medial OFC R | 0.143 | 0.167 | −0.101 | 0.163 | −0.234 | 0.690 | 0.015 | 0.171 | 1.018 | .287 |
| Medial OFC L | 0.140 | 0.178 | −0.099 | 0.157 | −0.211 | 0.684 | 0.015 | 0.167 | 1.001 | .319 |
| Inferior OFC R | 0.377 | 0.152 | −0.267 | 0.158 | 0.228 | 1.077 | 0.105 | 0.796 | 2.828 | .010[a] |
| Inferior OFC L | 0.424 | 0.175 | −0.300 | 0.143 | 0.309 | 1.151 | 0.133 | 0.888 | 3.224 | .005[a] |
| Dorsal Anterior Ins R | 0.432 | 0.168 | −0.305 | 0.146 | 0.324 | 1.174 | 0.138 | 0.901 | 3.293 | .002[a] |
| Dorsal Anterior Ins L | 0.381 | 0.177 | −0.270 | 0.145 | 0.198 | 1.103 | 0.107 | 0.805 | 2.858 | .009[a] |
| Ventral Anterior Ins R | 0.302 | 0.166 | −0.214 | 0.157 | 0.071 | 0.963 | 0.067 | 0.590 | 2.218 | .025[a] |
| Ventral Anterior Ins L | 0.421 | 0.177 | −0.298 | 0.141 | 0.288 | 1.154 | 0.131 | 0.884 | 3.199 | .007[a] |
| Posterior Ins R | 0.363 | 0.172 | −0.257 | 0.149 | 0.228 | 1.067 | 0.097 | 0.760 | 2.706 | .008[a] |
| Posterior Ins L | 0.405 | 0.182 | −0.287 | 0.140 | 0.269 | 1.132 | 0.121 | 0.855 | 3.063 | .004[a] |
| Caudate Head R | 0.239 | 0.164 | −0.169 | 0.161 | −0.030 | 0.829 | 0.042 | 0.401 | 1.733 | .075 |
| Caudate Head L | 0.138 | 0.189 | −0.098 | 0.150 | −0.268 | 0.747 | 0.014 | 0.164 | 0.987 | .327 |
| Putamen R | 0.319 | 0.174 | −0.226 | 0.151 | 0.128 | 1.019 | 0.075 | 0.641 | 2.354 | .022[a] |
| Putamen L | 0.259 | 0.200 | −0.183 | 0.138 | −0.022 | 0.933 | 0.049 | 0.457 | 1.879 | .071 |
| Ventral Striatum R | 0.141 | 0.193 | −0.100 | 0.148 | −0.230 | 0.717 | 0.015 | 0.168 | 1.006 | .336 |
| Ventral Striatum L | 0.164 | 0.192 | −0.116 | 0.148 | −0.190 | 0.747 | 0.020 | 0.211 | 1.171 | .259 |
| Nucleus Accumbens R | −0.020 | 0.166 | 0.014 | 0.165 | −0.502 | 0.413 | 0.000 | 0.052 | −0.141 | .909 |
| Nucleus Accumbens L | −0.075 | 0.179 | 0.053 | 0.158 | −0.608 | 0.346 | 0.004 | 0.082 | −0.534 | .590 |
| Receiving Sucrose Unexpectedly | | | | | | | | | | |
| Superior OFC R | 0.377 | 0.185 | −0.267 | 0.140 | 0.184 | 1.119 | 0.105 | 0.795 | 2.822 | .012[a] |
| Superior OFC L | 0.217 | 0.233 | −0.153 | 0.112 | −0.111 | 0.869 | 0.035 | 0.338 | 1.565 | .161 |
| Middle OFC R | 0.401 | 0.206 | −0.284 | 0.122 | 0.211 | 1.163 | 0.119 | 0.848 | 3.029 | .012[a] |
| Middle OFC L | 0.375 | 0.224 | −0.265 | 0.109 | 0.153 | 1.137 | 0.104 | 0.791 | 2.809 | .017[a] |
| Medial OFC R | 0.218 | 0.198 | −0.154 | 0.141 | −0.080 | 0.864 | 0.035 | 0.342 | 1.576 | .131 |
| Medial OFC L | 0.310 | 0.179 | −0.219 | 0.149 | 0.065 | 0.981 | 0.071 | 0.612 | 2.277 | .022[a] |
| Inferior OFC R | 0.375 | 0.194 | −0.265 | 0.134 | 0.183 | 1.105 | 0.104 | 0.790 | 2.808 | .011[a] |
| Inferior OFC L | 0.395 | 0.186 | −0.280 | 0.138 | 0.222 | 1.153 | 0.115 | 0.835 | 2.978 | .006[a] |
| Dorsal Anterior Ins R | 0.272 | 0.213 | −0.192 | 0.128 | 0.014 | 0.971 | 0.055 | 0.498 | 1.984 | .067 |
| Dorsal Anterior Ins L | 0.281 | 0.203 | −0.199 | 0.135 | 0.033 | 0.967 | 0.058 | 0.524 | 2.050 | .052 |
| Ventral Anterior Ins R | 0.316 | 0.194 | −0.223 | 0.139 | 0.113 | 1.034 | 0.074 | 0.631 | 2.326 | .032[a] |
| Ventral Anterior Ins L | 0.296 | 0.203 | −0.209 | 0.134 | 0.054 | 0.986 | 0.065 | 0.571 | 2.168 | .043[a] |
| Posterior Ins R | 0.116 | 0.232 | −0.082 | 0.117 | −0.288 | 0.680 | 0.010 | 0.128 | 0.823 | .445 |
| Posterior Ins L | 0.176 | 0.223 | −0.124 | 0.124 | −0.163 | 0.814 | 0.023 | 0.237 | 1.260 | .252 |
| Caudate Head R | 0.342 | 0.181 | −0.242 | 0.146 | 0.137 | 1.054 | 0.086 | 0.705 | 2.533 | .014[a] |
| Caudate Head L | 0.314 | 0.171 | −0.222 | 0.153 | 0.090 | 0.988 | 0.073 | 0.625 | 2.311 | .028[a] |
| Putamen R | 0.349 | 0.194 | −0.247 | 0.136 | 0.146 | 1.047 | 0.090 | 0.725 | 2.594 | .016[a] |
| Putamen L | 0.300 | 0.200 | −0.212 | 0.136 | 0.058 | 0.982 | 0.066 | 0.582 | 2.197 | .035[a] |
| Ventral Striatum R | 0.378 | 0.191 | −0.267 | 0.136 | 0.185 | 1.081 | 0.105 | 0.796 | 2.829 | .011[a] |
| Ventral Striatum L | 0.343 | 0.185 | −0.243 | 0.143 | 0.151 | 1.037 | 0.087 | 0.709 | 2.546 | .010[a] |
| Nucleus Accumbens R | 0.227 | 0.180 | −0.161 | 0.153 | −0.077 | 0.863 | 0.038 | 0.366 | 1.641 | .113 |
| Nucleus Accumbens L | 0.241 | 0.179 | −0.171 | 0.152 | −0.023 | 0.885 | 0.043 | 0.406 | 1.746 | .096 |
| Receiving No Solution Unexpectedly | | | | | | | | | | |
| Superior OFC R | −0.325 | 0.204 | 0.230 | 0.131 | −1.029 | −0.077 | 0.078 | 0.656 | −2.396 | .028[a] |
| Superior OFC L | −0.195 | 0.200 | 0.138 | 0.141 | −0.774 | 0.173 | 0.028 | 0.281 | −1.4 | .171 |
| Middle OFC R | −0.475 | 0.195 | 0.336 | 0.124 | −1.224 | −0.360 | 0.166 | 0.953 | −3.685 | .001[a] |

**Table 2. Continued**

| | Adolescents | | Adults | | 95% CI | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SE | Mean | SE | Lower | Upper | ES (Partial $\eta^2$) | Power | *t* | *p* Value |
| Middle OFC L | −0.328 | 0.216 | 0.232 | 0.121 | −1.028 | −0.075 | 0.079 | 0.666 | −2.422 | .027[a] |
| Medial OFC R | −0.236 | 0.173 | 0.167 | 0.156 | −0.840 | 0.039 | 0.041 | 0.39 | −1.704 | .082 |
| Medial OFC L | −0.184 | 0.190 | 0.130 | 0.148 | −0.760 | 0.158 | 0.025 | 0.256 | −1.322 | .195 |
| Inferior OFC R | −0.413 | 0.214 | 0.292 | 0.114 | −1.153 | −0.221 | 0.126 | 0.869 | −3.127 | .007[a] |
| Inferior OFC L | −0.359 | 0.211 | 0.254 | 0.122 | −1.084 | −0.143 | 0.095 | 0.75 | −2.671 | .013[a] |
| Dorsal Anterior Ins R | −0.415 | 0.209 | 0.293 | 0.119 | −1.150 | −0.228 | 0.127 | 0.873 | −3.145 | .007[a] |
| Dorsal Anterior Ins L | −0.358 | 0.210 | 0.253 | 0.124 | −1.078 | −0.115 | 0.095 | 0.748 | −2.667 | .015[a] |
| Ventral Anterior Ins R | −0.364 | 0.204 | 0.258 | 0.128 | −1.075 | −0.174 | 0.098 | 0.765 | −2.72 | .011[a] |
| Ventral Anterior Ins L | −0.372 | 0.210 | 0.263 | 0.122 | −1.076 | −0.149 | 0.102 | 0.783 | −2.783 | .019[a] |
| Posterior Ins R | −0.387 | 0.197 | 0.274 | 0.131 | −1.110 | −0.202 | 0.111 | 0.819 | −2.911 | .004[a] |
| Posterior Ins L | −0.321 | 0.213 | 0.227 | 0.124 | −1.010 | −0.068 | 0.076 | 0.644 | −2.363 | .029[a] |
| Caudate Head R | −0.291 | 0.199 | 0.206 | 0.137 | −0.986 | −0.033 | 0.063 | 0.557 | −2.133 | .048 |
| Caudate Head L | −0.231 | 0.215 | 0.164 | 0.128 | −0.899 | 0.079 | 0.039 | 0.378 | −1.672 | .123 |
| Putamen R | −0.498 | 0.191 | 0.352 | 0.123 | −1.281 | −0.419 | 0.183 | 0.971 | −3.905 | .003[a] |
| Putamen L | −0.458 | 0.207 | 0.324 | 0.115 | −1.220 | −0.326 | 0.155 | 0.936 | −3.529 | .004[a] |
| Ventral Striatum R | −0.392 | 0.208 | 0.277 | 0.122 | −1.154 | −0.193 | 0.113 | 0.828 | −2.95 | .011[a] |
| Ventral Striatum L | −0.382 | 0.214 | 0.270 | 0.117 | −1.137 | −0.188 | 0.108 | 0.807 | −2.868 | .011[a] |
| Nucleus Accumbens R | −0.224 | 0.204 | 0.159 | 0.137 | −0.875 | 0.103 | 0.037 | 0.359 | −1.621 | .122 |
| Nucleus Accumbens L | −0.198 | 0.215 | 0.140 | 0.129 | −0.833 | 0.133 | 0.029 | 0.29 | −1.425 | .200 |
| Receiving Sucrose Expectedly | | | | | | | | | | |
| Superior OFC R | 0.107 | 0.179 | −0.076 | 0.157 | −0.288 | 0.634 | 0.008 | 0.117 | 0.762 | .452 |
| Superior OFC L | −0.038 | 0.218 | 0.027 | 0.131 | −0.574 | 0.417 | 0.001 | 0.058 | −0.267 | .809 |
| Middle OFC R | −0.041 | 0.211 | 0.029 | 0.137 | −0.579 | 0.411 | 0.001 | 0.060 | −0.293 | .798 |
| Middle OFC L | −0.007 | 0.227 | 0.005 | 0.124 | −0.518 | 0.493 | 0.000 | 0.050 | −0.051 | .960 |
| Medial OFC R | −0.009 | 0.217 | 0.006 | 0.132 | −0.473 | 0.506 | 0.000 | 0.050 | −0.061 | .959 |
| Medial OFC L | 0.028 | 0.232 | −0.020 | 0.119 | −0.448 | 0.592 | 0.001 | 0.055 | 0.202 | .850 |
| Inferior OFC R | −0.010 | 0.200 | 0.007 | 0.145 | −0.492 | 0.453 | 0.000 | 0.051 | −0.073 | .945 |
| Inferior OFC L | −0.100 | 0.214 | 0.071 | 0.134 | −0.660 | 0.332 | 0.007 | 0.108 | −0.712 | .510 |
| Dorsal Anterior Ins R | −0.176 | 0.204 | 0.124 | 0.139 | −0.784 | 0.192 | 0.023 | 0.237 | −1.260 | .231 |
| Dorsal Anterior Ins L | −0.102 | 0.220 | 0.072 | 0.129 | −0.677 | 0.360 | 0.008 | 0.110 | −0.723 | .495 |
| Ventral Anterior Ins R | −0.164 | 0.201 | 0.116 | 0.142 | −0.764 | 0.180 | 0.020 | 0.211 | −1.170 | .274 |
| Ventral Anterior Ins L | −0.111 | 0.212 | 0.078 | 0.135 | −0.683 | 0.294 | 0.009 | 0.121 | −0.787 | .464 |
| Posterior Ins R | −0.138 | 0.212 | 0.098 | 0.134 | −0.712 | 0.287 | 0.014 | 0.163 | −0.984 | .330 |
| Posterior Ins L | −0.148 | 0.220 | 0.105 | 0.127 | −0.750 | 0.260 | 0.016 | 0.181 | −1.059 | .303 |
| Caudate Head R | 0.050 | 0.201 | −0.036 | 0.144 | −0.403 | 0.571 | 0.002 | 0.064 | 0.358 | .738 |
| Caudate Head L | 0.071 | 0.196 | −0.050 | 0.147 | −0.368 | 0.594 | 0.004 | 0.079 | 0.503 | .632 |
| Putamen R | −0.022 | 0.211 | 0.016 | 0.137 | −0.528 | 0.457 | 0.000 | 0.053 | −0.159 | .876 |
| Putamen L | −0.026 | 0.220 | 0.018 | 0.130 | −0.541 | 0.471 | 0.000 | 0.054 | −0.184 | .851 |
| Ventral Striatum R | 0.073 | 0.213 | −0.051 | 0.135 | −0.387 | 0.619 | 0.004 | 0.080 | 0.516 | .657 |
| Ventral Striatum L | 0.053 | 0.209 | −0.038 | 0.139 | −0.421 | 0.584 | 0.002 | 0.066 | 0.377 | .743 |
| Nucleus Accumbens R | 0.108 | 0.204 | −0.077 | 0.141 | −0.296 | 0.671 | 0.009 | 0.118 | 0.770 | .473 |
| Nucleus Accumbens L | 0.136 | 0.193 | −0.096 | 0.148 | −0.271 | 0.715 | 0.014 | 0.160 | 0.973 | .354 |

CI, confidence interval; ES, effect size; Ins, insula; L, left; OFC, orbitofrontal cortex; R, right.
[a]These *p* values remained significant after multiple comparison correction.

insula and striatal regions, and between FC and CC; adults also showed a cluster of correlation between FC and insula (Figure 1).

**Unexpected Sucrose Receipt.** Both groups showed significant correlations within anatomically related ROIs, and between FC regions and inferior OFC and the CC regions; adolescents showed a large cluster of correlation between FC and striatal ROIs.

**Unexpected Sucrose Omission.** Both groups showed significant correlations within anatomically related ROIs as well

**Table 3. Brain-Temperament Trait Correlation Results**

| | | Adolescent Girls | | | Adult Women | | | | Group Contrast | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | RD | P | SR | RD | P | SR | *p* or *z* | RD | P | SR |
| Prediction Error Correlation Age, BMI Adjusted | | | | | | | | | | | |
| Superior OFC R | *r* | 0.028 | 0.243 | 0.003 | −0.098 | 0.067 | 0.070 | *z* | | | |
| | *p* | .890 | .221 | .986 | .554 | .687 | .671 | *p* | | | |
| Superior OFC L | *r* | 0.090 | 0.509 | 0.307 | −0.204 | 0.123 | −0.022 | *z* | | 1.720 | |
| | *p* | .657 | .007[a] | .119 | .212 | .457 | .894 | *p* | | .043[a] | |
| Middle OFC R | *r* | 0.217 | 0.219 | 0.136 | −0.128 | 0.023 | −0.159 | *z* | | | |
| | *p* | .276 | .273 | .497 | .438 | .887 | .335 | *p* | | | |
| Middle OFC L | *r* | 0.149 | 0.429 | 0.312 | −0.293 | 0.053 | −0.064 | *z* | | | |
| | *p* | .458 | .026[a] | .113 | .070 | .748 | .697 | *p* | | | |
| Medial OFC R | *r* | 0.176 | 0.267 | 0.133 | 0.144 | 0.033 | −0.028 | *z* | | | |
| | *p* | .379 | .179 | .507 | .383 | .840 | .867 | *p* | | | |
| Medial OFC L | *r* | 0.093 | 0.102 | 0.128 | 0.197 | 0.064 | 0.188 | *z* | | | |
| | *p* | .645 | .612 | .524 | .230 | .700 | .252 | *p* | | | |
| Inferior OFC R | *r* | 0.288 | 0.278 | 0.133 | −0.139 | −0.066 | 0.028 | *z* | | | |
| | *p* | .145 | .160 | .509 | .399 | .690 | .864 | *p* | | | |
| Inferior OFC L | *r* | 0.169 | 0.553 | 0.331 | −0.248 | −0.142 | −0.079 | *z* | | 3.008 | |
| | *p* | .399 | .003[a] | .092 | .127 | .388 | .632 | *p* | | .001[a] | |
| Dorsal Anterior Ins R | *r* | 0.040 | 0.248 | −0.104 | −0.147 | −0.032 | −0.056 | *z* | | | |
| | *p* | .842 | .213 | .607 | .373 | .849 | .736 | *p* | | | |
| Dorsal Anterior Ins L | *r* | 0.245 | 0.584 | −0.022 | −0.163 | −0.065 | −0.076 | *z* | | 2.882 | |
| | *p* | .219 | .001[a] | .914 | .321 | .695 | .644 | *p* | | .002[a] | |
| Ventral Anterior Ins R | *r* | 0.185 | 0.329 | 0.106 | 0.070 | −0.049 | 0.127 | *z* | | | |
| | *p* | .357 | .094 | .599 | .671 | .766 | .442 | *p* | | | |
| Ventral Anterior Ins L | *r* | 0.084 | 0.490 | 0.113 | −0.127 | −0.049 | 0.128 | *z* | | 2.299 | |
| | *p* | .677 | .009[a] | .576 | .442 | .768 | .439 | *p* | | .011[a] | |
| Posterior Ins R | *r* | 0.160 | 0.232 | −0.078 | −0.025 | 0.154 | 0.089 | *z* | | | |
| | *p* | .426 | .244 | .699 | .879 | .350 | .590 | *p* | | | |
| Posterior Ins L | *r* | 0.139 | 0.515 | 0.026 | −0.113 | 0.086 | 0.145 | *z* | | 1.899 | |
| | *p* | .490 | .006[a] | .896 | .495 | .601 | .378 | *p* | | .029[a] | |
| Caudate Head R | *r* | 0.118 | 0.405 | −0.032 | −0.215 | −0.004 | −0.030 | *z* | | 1.704 | |
| | *p* | .556 | .036[a] | .874 | .189 | .981 | .858 | *p* | | .044[a] | |
| Caudate Head L | *r* | 0.107 | 0.504 | −0.099 | −0.188 | −0.031 | −0.161 | *z* | | 2.301 | |
| | *p* | .596 | .007[a] | .623 | .253 | .849 | .329 | *p* | | .011[a] | |
| Putamen R | *r* | 0.033 | 0.238 | −0.201 | −0.377 | 0.128 | −0.019 | *z* | | | |
| | *p* | .871 | .232 | .315 | .018 | .436 | .907 | *p* | | | |
| Putamen L | *r* | 0.132 | 0.591 | 0.017 | −0.275 | 0.136 | 0.001 | *z* | | 2.131 | |
| | *p* | .511 | .001[a] | .934 | .091 | .408 | .994 | *p* | | .017[a] | |
| Ventral Striatum R | *r* | 0.212 | 0.343 | −0.150 | −0.328 | 0.084 | 0.072 | *z* | | | |
| | *p* | .289 | .080 | .455 | .042 | .613 | .662 | *p* | | | |
| Ventral Striatum L | *r* | 0.157 | 0.497 | −0.014 | −0.137 | 0.206 | 0.008 | *z* | | | |
| | *p* | .435 | .008[a] | .945 | .407 | .209 | .964 | *p* | | | |
| Nucleus Accumbens R | *r* | 0.141 | 0.374 | −0.077 | −0.055 | −0.012 | 0.094 | *z* | | | |
| | *p* | .484 | .055 | .702 | .739 | .942 | .570 | *p* | | | |
| Nucleus Accumbens L | *r* | 0.157 | 0.423 | −0.031 | −0.027 | −0.062 | −0.099 | *z* | | 2.017 | |
| | *p* | .435 | .028[a] | .878 | .870 | .708 | .550 | *p* | | .022[a] | |
| Unexpected Receipt Correlation Age, BMI Adjusted | | | | | | | | | | | |
| Superior OFC R | *r* | 0.515 | 0.346 | −0.141 | 0.054 | 0.055 | −0.093 | *z* | 2.025 | | |
| | *p* | .006[a] | .077 | .482 | .744 | .739 | .575 | *p* | .021[a] | | |
| Superior OFC L | *r* | 0.516 | 0.437 | 0.138 | −0.198 | .066 | −0.269 | *z* | 3.031 | | |
| | *p* | .006[a] | .023[a] | .492 | .226 | .689 | .098 | *p* | .001[a] | | |

**Table 3. Continued**

| | | Adolescent Girls | | | Adult Women | | | | Group Contrast | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | RD | P | SR | RD | P | SR | *p* or *z* | RD | P | SR |
| Middle OFC R | *r* | 0.266 | 0.342 | 0.114 | −0.042 | 0.064 | 0.036 | *z* | | | |
| | *p* | .180 | .081 | .570 | .800 | .701 | .829 | *p* | | | |
| Middle OFC L | *r* | 0.354 | 0.466 | 0.234 | −0.084 | −0.017 | −0.026 | *z* | | 2.051 | |
| | *p* | .070 | .014[a] | .241 | .613 | .918 | .875 | *p* | | .020[a] | |
| Medial OFC R | *r* | 0.235 | 0.262 | −0.033 | −0.195 | 0.208 | −0.101 | *z* | | | |
| | *p* | .238 | .186 | .870 | .235 | .204 | .539 | *p* | | | |
| Medial OFC L | *r* | 0.069 | 0.326 | 0.041 | 0.118 | 0.351 | 0.008 | *z* | | | |
| | *p* | .734 | .097 | .838 | .473 | .029 | .963 | *p* | | | |
| Inferior OFC R | *r* | 0.161 | 0.412 | −0.018 | 0.008 | −0.031 | −0.023 | *z* | | 1.843 | |
| | *p* | .424 | .033[a] | .930 | .962 | .850 | .889 | *p* | | .033[a] | |
| Inferior OFC L | *r* | 0.428 | 0.405 | 0.222 | 0.067 | −0.130 | −0.002 | *z* | | 2.202 | |
| | *p* | .026[a] | .036[a] | .266 | .685 | .430 | .992 | *p* | | .014[a] | |
| Dorsal Anterior Ins R | *r* | 0.205 | 0.182 | 0.064 | 0.095 | −0.158 | −0.320 | *z* | | | |
| | *p* | .306 | .364 | .751 | .566 | .337 | .047 | *p* | | | |
| Dorsal Anterior Ins L | *r* | 0.421 | 0.384 | 0.159 | 0.055 | −0.115 | −0.324 | *z* | | 2.044 | |
| | *p* | .029[a] | .048[a] | .430 | .741 | .485 | .044 | *p* | | .020[a] | |
| Ventral Anterior Ins R | *r* | 0.152 | 0.319 | 0.032 | 0.021 | −0.023 | −0.109 | *z* | | | |
| | *p* | .448 | .105 | .872 | .899 | .888 | .510 | *p* | | | |
| Ventral Anterior Ins L | *r* | 0.417 | 0.444 | 0.094 | 0.079 | −0.012 | −0.074 | *z* | | 1.922 | |
| | *p* | .030[a] | .020[a] | .642 | .634 | .942 | .656 | *p* | | .027[a] | |
| Posterior Ins R | *r* | 0.194 | 0.091 | 0.004 | −0.045 | 0.084 | −0.142 | *z* | | | |
| | *p* | .332 | .650 | .985 | .786 | .611 | .389 | *p* | | | |
| Posterior Ins L | *r* | 0.158 | 0.397 | 0.055 | 0.044 | 0.055 | −0.019 | *z* | | | |
| | *p* | .432 | .040[a] | .786 | .788 | .741 | .909 | *p* | | | |
| Caudate Head R | *r* | 0.079 | 0.157 | −0.137 | −0.273 | −0.211 | −0.040 | *z* | | | |
| | *p* | .696 | .433 | .495 | .093 | .197 | .809 | *p* | | | |
| Caudate Head L | *r* | 0.167 | 0.137 | −0.059 | −0.217 | −0.233 | −0.107 | *z* | | | |
| | *p* | .406 | .495 | .771 | .185 | .153 | .515 | *p* | | | |
| Putamen R | *r* | 0.198 | 0.209 | −0.022 | −0.058 | −0.026 | −0.170 | *z* | | | |
| | *p* | .321 | .296 | .913 | .727 | .874 | .302 | *p* | | | |
| Putamen L | *r* | 0.151 | 0.274 | 0.043 | −0.013 | −0.046 | −0.235 | *z* | | | |
| | *p* | .453 | .166 | .832 | .939 | .782 | .149 | *p* | | | |
| Ventral Striatum R | *r* | 0.253 | 0.329 | 0.020 | −0.028 | 0.028 | −0.136 | *z* | | | |
| | *p* | .203 | .094 | .919 | .864 | .864 | .409 | *p* | | | |
| Ventral Striatum L | *r* | 0.232 | 0.312 | 0.076 | 0.010 | 0.065 | −0.220 | *z* | | | |
| | *p* | .244 | .113 | .708 | .952 | .693 | .179 | *p* | | | |
| Nucleus Accumbens R | *r* | 0.153 | 0.257 | −0.069 | −0.186 | −0.223 | −0.112 | *z* | | | |
| | *p* | .445 | .196 | .732 | .256 | .172 | .495 | *p* | | | |
| Nucleus Accumbens L | *r* | 0.209 | 0.296 | 0.051 | −0.124 | −0.194 | −0.151 | *z* | | | |
| | *p* | .295 | .134 | .802 | .451 | .237 | .357 | *p* | | | |
| Unexpected Omission Correlation Age, BMI Adjusted | | | | | | | | | | | |
| Superior OFC R | *r* | −0.161 | −0.617 | −0.286 | −0.138 | 0.039 | −0.162 | *z* | | −2.983 | |
| | *p* | .422 | .001[a] | .148 | .402 | .815 | .326 | *p* | | .001[a] | |
| Superior OFC L | *r* | −0.313 | −0.559 | −0.322 | −0.156 | 0.076 | 0.009 | *z* | | −2.78 | |
| | *p* | .111 | .002[a] | .102 | .344 | .646 | .955 | *p* | | .003[a] | |
| Middle OFC R | *r* | −0.342 | −0.540 | −0.317 | 0.002 | 0.056 | 0.059 | *z* | | −2.594 | |
| | *p* | .081 | .004[a] | .108 | .99 | .735 | .721 | *p* | | .005[a] | |
| Middle OFC L | *r* | −0.412 | −0.577 | −0.325 | −0.323 | 0.002 | 0.122 | *z* | | −2.593 | |
| | *p* | .033[a] | .002[a] | .098 | .045 | .991 | .459 | *p* | | .005[a] | |
| Medial OFC R | *r* | −0.332 | −0.447 | −0.209 | −0.055 | −0.073 | −0.073 | *z* | | −2.165 | |
| | *p* | .091 | .019[a] | .295 | .741 | .658 | .659 | *p* | | .015[a] | |

**Table 3. Continued**

| | | Adolescent Girls | | | Adult Women | | | | Group Contrast | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | RD | P | SR | RD | P | SR | *p* or *z* | RD | P | SR |
| Medial OFC L | *r* | −0.222 | −0.483 | −0.272 | −0.106 | −0.232 | −0.056 | *z* | | −2.99 | |
| | *p* | .265 | .011[a] | .169 | .519 | .155 | .737 | *p* | | .001[a] | |
| Inferior OFC R | *r* | −0.524 | −0.576 | −0.389 | 0.006 | −0.114 | 0.018 | *z* | −2.31 | −3.013 | −1.684 |
| | *p* | .005[a] | .002[a] | .045[a] | .969 | .49 | .911 | *p* | .01[a] | .001[a] | .046[a] |
| Inferior OFC L | *r* | −0.514 | −0.551 | −0.490 | −0.335 | −0.161 | −0.039 | *z* | | −3.069 | −1.949 |
| | *p* | .006[a] | .003[a] | .010[a] | .037 | .329 | .812 | *p* | | .001[a] | .026[a] |
| Dorsal Anterior Ins R | *r* | −0.421 | −0.383 | −0.339 | 0.001 | 0.081 | 0.001 | *z* | −1.768 | −1.905 | |
| | *p* | .029[a] | .048[a] | .084 | .996 | .625 | .994 | *p* | .039[a] | .028[a] | |
| Dorsal Anterior Ins L | *r* | −0.321 | −0.505 | −0.384 | −0.232 | −0.01 | −0.02 | *z* | | −2.145 | |
| | *p* | .103 | .007[a] | .048[a] | .156 | .95 | .905 | *p* | | .016[a] | |
| Ventral Anterior Ins R | *r* | −0.456 | −0.506 | −0.410 | −0.061 | −0.004 | −0.04 | *z* | −1.694 | −2.19 | |
| | *p* | .017[a] | .007[a] | .034[a] | .712 | .981 | .807 | *p* | .045[a] | .014[a] | |
| Ventral Anterior Ins L | *r* | −0.405 | −0.475 | −0.346 | −0.211 | −0.12 | −0.114 | *z* | | | |
| | *p* | .036 | .012[a] | .077 | .198 | .466 | .491 | *p* | | | |
| Posterior Ins R | *r* | −0.285 | −0.229 | −0.287 | −0.034 | −0.065 | −0.007 | *z* | | | |
| | *p* | .15 | .250[a] | .146 | .839 | .694 | .967 | *p* | | | |
| Posterior Ins L | *r* | −0.296 | −0.488 | −0.417 | −0.098 | −0.013 | 0.005 | *z* | | −2.045 | −1.764 |
| | *p* | .133 | .010[a] | .031[a] | .551 | .936 | .978 | *p* | | .02[a] | .039[a] |
| Caudate Head R | *r* | −0.464 | −0.537 | −0.439 | 0.01 | 0.112 | 0.027 | *z* | −2.013 | −2.799 | −1.957 |
| | *p* | .015[a] | .004[a] | .022[a] | .953 | .498 | .871 | *p* | .022[a] | .003[a] | .025[a] |
| Caudate Head L | *r* | −0.422 | −0.466 | −0.437 | 0.117 | 0.161 | 0.051 | *z* | −2.23 | −2.622 | −2.041 |
| | *p* | .028[a] | .014[a] | .023[a] | .476 | .327 | .757 | *p* | .013[a] | .004[a] | .021[a] |
| Putamen R | *r* | −0.382 | −0.462 | −0.342 | 0.071 | 0.012 | −0.075 | *z* | −1.86 | −2.011 | |
| | *p* | .049[a] | .015[a] | .080 | .669 | .94 | .648 | *p* | .031[a] | .022[a] | |
| Putamen L | *r* | −0.38 | −0.529 | −0.397 | −0.087 | 0.032 | −0.029 | *z* | | −2.439 | −1.768 |
| | *p* | .051 | .005[a] | .040[a] | .6 | .847 | .861 | *p* | | .007[a] | .038[a] |
| Ventral Striatum R | *r* | −0.475 | −0.462 | −0.306 | −0.006 | −0.034 | −0.166 | *z* | −2.006 | −2.082 | |
| | *p* | .012[a] | .015[a] | .121 | .973 | .839 | .311 | *p* | .022[a] | .019[a] | |
| Ventral Striatum L | *r* | −0.502 | −0.629 | −0.332 | −0.189 | 0.002 | −0.08 | *z* | | −2.914 | |
| | *p* | .008[a] | <.001[a] | .091 | .248 | .99 | .627 | *p* | | .002[a] | |
| Nucleus Accumbens R | *r* | −0.475 | −0.429 | −0.296 | −0.13 | 0.062 | 0.033 | *z* | | −2.046 | |
| | *p* | .012[a] | .026[a] | .134 | .43 | .706 | .843 | *p* | | .02[a] | |
| Nucleus Accumbens L | *r* | −0.376 | −0.523 | −0.330 | −0.107 | 0.068 | 0.116 | *z* | | −2.548 | |
| | *p* | .053 | .005[a] | .092 | .517 | .682 | .481 | *p* | | .005[a] | |

BMI, body mass index; Ins, insula; L, left; OFC, orbitofrontal cortex; P, persistence; RD, reward dependence; R, right; SR, reward sensitivity.
[a]These *p* values remained significant after multiple comparison correction.

as between FC and CC; adolescents but not adults showed correlation clusters between FC or OFC and striatum.

**Expected Sucrose Receipt.** Both groups showed significant correlations within anatomically related ROIs as well as between FC and CC, insula, and striatum, and between CC and insula and striatum, which was denser in adults.

After adjusting in both groups for persistence using partial correlation analysis, the striatal-FC correlations vanished in the adolescent group for unexpected stimulus omission.

## DISCUSSION

This study supports that adolescents show higher prediction error response than adults, primarily located in the insula and OFC. Adolescents also responded more strongly during the unexpected stimulus receipt and omission conditions across the insula, OFC, and striatum, while response to expected receipt was similar between groups. Persistence was associated with prediction error response, and response to unexpected stimulus receipt and omission in adolescents but not in adults. Reward dependence and reward sensitivity were associated with unexpected stimulus receipt or omission in adolescents. Maps of associated brain regions indicated for unexpected receipt and omission strong relationships between striatal and FC activation in adolescents that were moderated by the persistence score. The study emphasizes the importance of the trait persistence in adolescent girls in the context of reward response. This temperamental trait could be a moderator of adaptive

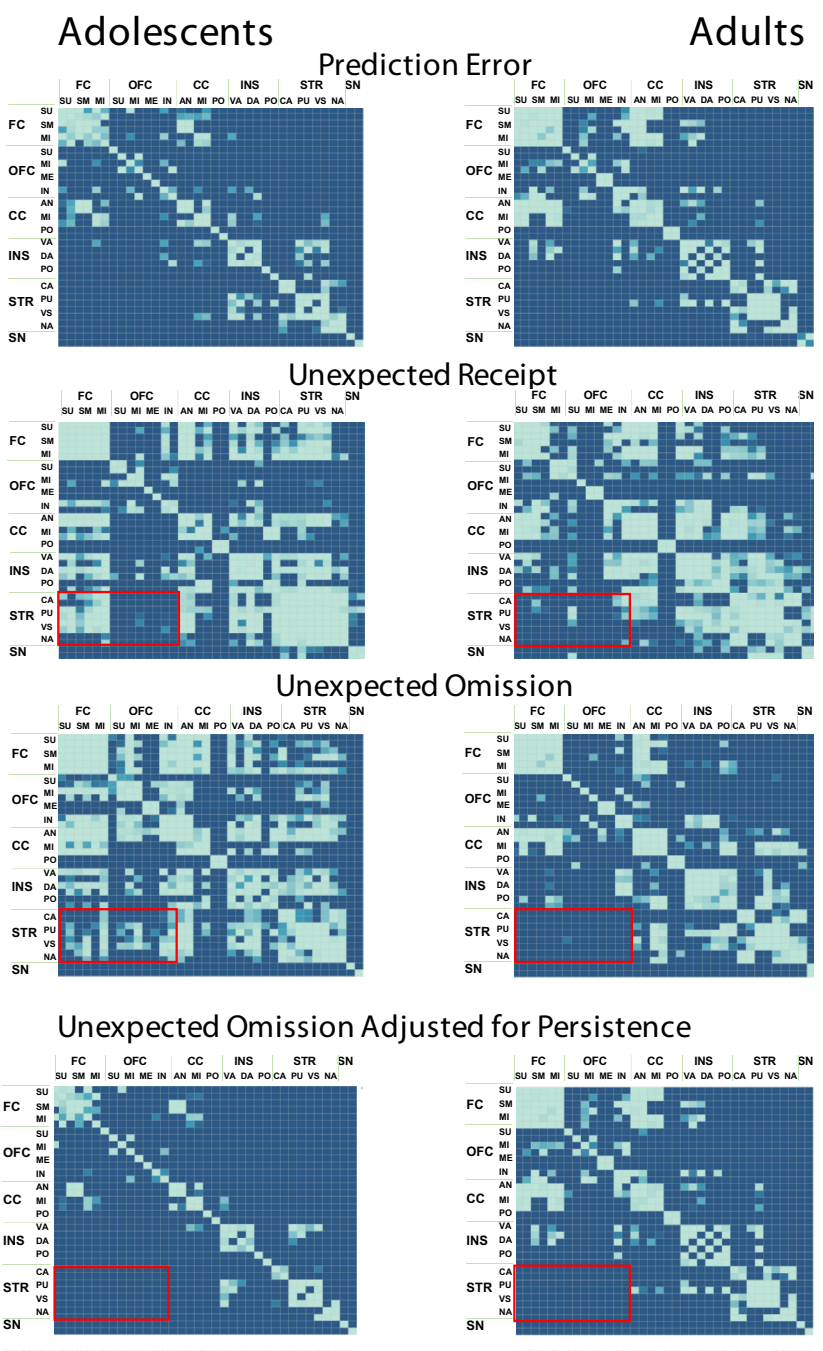


**Figure 1.** Regional activation correlation maps. All light green squares indicate Bonferroni-corrected significant correlations ($p < .000009$). The red box indicates where striatal-frontal and orbitofrontal cortex (OFC) correlations are displayed. AN, anterior; CA, caudate head; CC, cingulate cortex; DA, dorsal anterior; FC, frontal cortex; IN, inferior; INS, insula; ME, medial; MI, middle; NA, nucleus accumbens; PO, posterior; PU, putamen; SM, superior medial; SN, substantia nigra; STR, striatum; SU, superior; VA, ventral anterior; VS, ventral striatum.

learning that provides protection from or poses risk in that age group and should be investigated further.

## Group Contrasts for Reward Brain Response

Both study groups responded with positive brain activation to unexpected stimulus receipt and negative response to unexpected omission (32). The adolescent females' brain response was stronger during the prediction error task compared with adults' (12,14). The responses to unexpected stimulus receipt or omission were also elevated in this sample of adolescent females. Prediction error response group differences were primarily in the OFC and insula, while for expected receipt and omission, bilateral putamen and ventral striatum responses also separated groups. Bilateral middle and inferior OFC and ventral anterior insula differentiated groups across all three conditions. This suggests that the dopamine-related prediction

error response has already matured largely to adult levels in striatal regions, but other circuitry contributing to unexpectancy response in OFC and insula is still developing, while response to expected stimulus receipt had developed in adolescents in our sample.

## Group Contrasts for Brain Response–Temperament Correlations

We had hypothesized that novelty seeking, persistence, and reward sensitivity would be positively correlated with prediction error response in adolescents as a sign of impulsive, reward-oriented behavior (42). Persistence in adolescents versus adults emerged as more strongly and positively correlated with prediction error response (left superior and inferior OFC, left dorsal anterior and ventral anterior and posterior insula, bilateral caudate, left putamen, nucleus accumbens) and with unexpected stimulus receipt response (left middle and bilateral inferior OFC, left dorsal and ventral anterior insula). Most pronounced, however, was persistence score that was negatively correlated with unexpected stimulus omission response across all regions except for left ventral anterior and right posterior insula. One previous study in adults linked persistence to orbito- and prefrontal cortical brain circuitry during emotional picture viewing, but we are not aware of studies in youth (43).

Individuals high in persistence show perfectionistic perseveration in response to intermittent reinforcement and are ambitious and overachieving in response to intermittent frustrative nonreward (30). High persistence is "an adaptive behavioral strategy when rewards are intermittent and the contingencies remain stable; however, when contingencies change rapidly, perseveration becomes maladaptive" (30). Elevated persistence has been associated with eating disorders, while lower persistence scores were found in depression; persistence has also been linked to suicidal behavior (44–47). Our results suggest that more persistent adolescents respond stronger to reward conditions where the expectation is violated, and this is most pronounced for the unexpected omission condition. Reward pathway response and temperament are connected, and it is possible that adolescents with a temperament that is characterized by high persistence could have difficulties adapting to new life situations and developing new adaptive behaviors (48).

In addition, the higher an adolescent scored on reward sensitivity, the stronger was the negative response to unexpected stimulus omission in the inferior OFC, left posterior insula, bilateral caudate, and left putamen. Higher reward dependence was associated with stronger response to unexpected stimulus receipt in the superior OFC in adolescent females and unexpected omission in the right inferior OFC, dorsal and ventral anterior insula, bilateral caudate, and right ventral striatum. The results suggest that reward sensitivity and reward dependence are also relevant for unexpectancy reward response in adolescents, but less specific to the dopamine-related prediction error.

Brain neurocircuitry undergoes significant changes until reaching adulthood, while temperamental traits are relatively stable (22). The former includes the dopamine-related prediction error response as an important learning signal for response to future reward situations (49). We propose that a typical adolescent responds to unexpected reward omission with a strong biological response that could be consistent with "disappointment," but that with the transition to adulthood that individual adapts to this type of situation and learns to regulate negative emotions around that situation, and the strong reward-circuit response habituates and becomes less pronounced. However, the more a person's temperament is characterized by persistence (a mindset of "I am still going to get it"), the stronger the brain response may be, and the more that person may have difficulties with adaptation to the frustrative nonreward situation. This could lead to, for instance, excessive frustration, low mood, or anxiety to stimulus omission but maybe also excessive seeking of reward stimuli. Studies on developmental psychopathology are limited, but recent research emphasized the intersection between intrapsychic and environmental factors and reward processing, and it is possible that persistence plays a mediating role (50,51).

The adult group showed inverse correlations between harm avoidance scores and superior and middle OFC prediction error response. The more anxious those adults were, the lower the prediction error response. Harm avoidance is a trait that describes individuals who are overly cautious, apprehensive, nervous, or pessimistic even in situations that do not worry other people (30). Anxious individuals may have learned to control or temper reward responses, with the exaggerated fear of a potentially negative outcome, even in light of a reward.

Taste pleasantness correlated inversely with predictable sweet stimulus receipt in both groups across frontal, insular, and subcortical regions, suggesting that this aspect of taste valence is already well established in adolescents and comparable to that in adults. Sweetness perception was more negatively correlated in adolescents with expected sucrose receipt in orbitofrontal, cingulate, and insular regions. In adolescents, sweetness and pleasantness perception of the applied 1M sucrose solution were not significantly correlated ($r$ = 0.209, $p$ = .276), while in adults, there was a strong negative correlation ($r$ = −0.429, $p$ = .005). The applied 1M sucrose contains about three times the sugar concentration of common fruit juice and is therefore extremely sweet. Adults' responses indicated that very high sweetness was not pleasant. The adolescents may not have had established that relationship, supporting the notion that taste perception and valuation are still developing at that age.

## ROI Correlation Maps

Regional correlations were comparable between groups for prediction error and expected stimulus receipt. For unexpected stimulus receipt and omission, adolescents showed significant correlation clusters between the striatum and frontal and orbitofrontal cortices that were much less or were absent in adults. This suggests extensive activation of higher-order cognitive circuits in the context of unexpectancy in adolescent females. Controlling for persistence, those correlations did not remain significant. Persistence could be an important temperament trait that affects brain biology and reward learning especially during adolescence, moderating the

connection between subcortical reward system response and cognitive-emotional circuitry and presumably learning.

## Limitations

The study groups consisted only of females, and a study in males is needed. Study group sizes were not entirely matched, but significant group differences were controlled for multiple comparisons, and effect sizes and power were high. The study sample was primarily Caucasian, limiting its generalizability to other races or more socioeconomically diverse groups (52). The anatomical ROI-based stringent analysis methods were aimed to provide reliable results. Nevertheless, a study on whole-brain fMRI behavior correlations suggested that a sample size of approximately 80 is needed for reproducible results, and our study results need replication (53). We chose a sweet-taste task, and tasks that study social rewards could yield different results. The unsigned prediction error may rather test the motivational salience aspect of this circuitry and be less related to the valuation ("better or worse than expected") of the stimulus (54,55). Recent studies have implicated the unsigned prediction error in learning, although the original model associated signed prediction error with learning response (54,56,57). The reward prediction error model has been strongly associated with the dopamine circuitry, but we did not directly test the dopamine system, and other neurotransmitters are likely involved (54).

## Conclusions

This study highlights the importance of persistence as a temperamental trait in adolescent development. We propose that persistence is a stable trait that moderates dopamine-related brain reward response to unexpected reward contingencies in adolescence. Those relationships between temperamental traits and neurobiology may become key elements of understanding learning in the normal transition from adolescence to adulthood as well as for understanding vulnerability for psychiatric illness.

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## ARTICLE INFORMATION

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## REFERENCES

1. McAdams DP, Olson BD (2010): Personality development: Continuity and change over the life course. Annu Rev Psychol 61:517–542.
2. Rothbart MK, Ahadi SA (1994): Temperament and the development of personality. J Abnorm Psychol 103:55–66.
3. Paus T, Keshavan M, Giedd JN (2008): Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci 9:947–957.
4. Borodinsky LN, Belgacem YH, Swapna I, Sequerra EB (2014): Dynamic regulation of neurotransmitter specification: Relevance to nervous system homeostasis. Neuropharmacology 78:75–80.
5. Suri D, Teixeira CM, Cagliostro MK, Mahadevia D, Ansorge MS (2015): Monoamine-sensitive developmental periods impacting adult emotional and cognitive behaviors. Neuropsychopharmacology 40:88–112.
6. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005): Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National comorbidity Survey Replication. Arch Gen Psychiatry 62:593–602.
7. Eaton NR, Keyes KM, Krueger RF, Balsis S, Skodol AE, Markon KE, *et al.* (2012): An invariant dimensional liability model of gender differences in mental disorder prevalence: Evidence from a national sample. J Abnorm Psychol 121:282–288.
8. Chaplin TM, Aldao A (2013): Gender differences in emotion expression in children: A meta-analytic review. Psychol Bull 139:735–765.
9. Dorfman J, Rosen D, Pine D, Ernst M (2016): Anxiety and gender influence reward-related processes in children and adolescents. J Child Adolesc Psychopharmacol 26:380–390.
10. Zahn-Waxler C, Crick N, Shirtcliff E, Woods K (2015): The origins and development of psychopathology in females and males. In: Cicchetti D, Cohen D, editors. Developmental Psychopathology: Volume 1: Theory and Method, 2nd ed.. ( 76–138). Hoboken, NJ: John Wiley & Sons, Inc., 76–138
11. Ernst M, Pine DS, Hardin M (2006): Triadic model of the neurobiology of motivated behavior in adolescence. Psychol Med 36:299–312.
12. Cohen JR, Asarnow RF, Sabb FW, Bilder RM, Bookheimer SY, Knowlton BJ, Poldrack RA (2010): A unique adolescent response to reward prediction errors. Nat Neurosci 13:669–671.
13. O'Doherty JP, Cockburn J, Pauli WM (2017): Learning, reward, and decision making. Annu Rev Psychol 68:73–100.
14. Cao Z, Bennett M, Orr C, Icke I, Banaschewski T, Barker GJ, *et al.* (2019): Mapping adolescent reward anticipation, receipt, and prediction error during the monetary incentive delay task. Hum Brain Mapp 40:262–283.
15. Bakker JM, Goossens L, Kumar P, Lange IMJ, Michielse S, Schruers K, *et al.* (2019): From laboratory to life: Associating brain reward processing with real-life motivated behaviour and symptoms of depression in non-help-seeking young adults. Psychol Med 49:2441–2451.
16. Frank GKW, DeGuzman MC, Shott ME, Laudenslager ML, Rossi B, Pryor T (2018): Association of brain reward learning response with harm avoidance, weight gain, and hypothalamic effective connectivity in adolescent anorexia nervosa. JAMA Psychiatry 75:1071–1080.
17. Ernst M, Romeo RD, Andersen SL (2009): Neurobiology of the development of motivated behaviors in adolescence: A window into a neural systems model. Pharmacol Biochem Behav 93:199–211.
18. Fairchild G (2011): The developmental psychopathology of motivation in adolescence. Dev Cogn Neurosci 1:414–429.
19. Schultz W (2017): Reward prediction error. Curr Biol 27:R369–R371.
20. Calkins SD, Dollar JM, Wideman L (2019): Temperamental vulnerability to emotion dysregulation and risk for mental and physical health challenges. Dev Psychopathol 31:957–970.
21. Keren H, Chen G, Benson B, Ernst M, Leibenluft E, Fox NA, *et al.* (2018): Is the encoding of reward prediction error reliable during development? Neuroimage 178:266–276.
22. Garcia D, Lundström S, Brändström S, Råstam M, Cloninger CR, Kerekes N, *et al.* (2013): Temperament and character in the Child and Adolescent Twin Study in Sweden (CATSS): Comparison to the general population, and genetic structure analysis. PLoS One 8: e70475.

23. Geier C, Luna B (2009): The maturation of incentive processing and cognitive control. Pharmacol Biochem Behav 93:212–221.
24. Cloninger CR, Cloninger KM, Zwir I, Keltikangas-Järvinen L (2019): The complex genetics and biology of human temperament: A review of traditional concepts in relation to new molecular findings. Transl Psychiatry 9:290.
25. White LK, McDermott JM, Degnan KA, Henderson HA, Fox NA (2011): Behavioral inhibition and anxiety: The moderating roles of inhibitory control and attention shifting. J Abnorm Child Psychol 39:735–747.
26. Wessman J, Schönauer S, Miettunen J, Turunen H, Parviainen P, Seppänen JK, *et al.* (2012): Temperament clusters in a normal population: Implications for health and disease. PLoS One 7:e33088.
27. Kim SH, Yoon H, Kim H, Hamann S (2015): Individual differences in sensitivity to reward and punishment and neural activity during reward and avoidance learning. Soc Cogn Affect Neurosci 10:1219–1227.
28. Panek-Scarborough LM, Dewey AM, Temple JL (2012): Sensation and perception of sucrose and fat stimuli predict the reinforcing value of food. Physiol Behav 105:1242–1249.
29. Sheehan DV, Sheehan KH, Shytle RD, Janavs J, Bannon Y, Rogers JE, *et al.* (2010): Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J Clin Psychiatry 71:313–326.
30. Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD (1994): The Temperament and Character Inventory (TCI): A Guide to Its Development and Use. St Louis, MO: Center for Psychobiology of Personality, Washington University.
31. Torrubia R, Ávila C, Moltó J, Caseras X (2001): The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Pers Individ Dif 31:837–862.
32. O'Doherty JP, Dayan P, Friston K, Critchley H, Dolan RJ (2003): Temporal difference models and reward-related learning in the human brain. Neuron 38:329–337.
33. Frank GK, Kaye WH, Carter CS, Brooks S, May C, Fissell K, Stenger VA (2003): The evaluation of brain activity in response to taste stimuli—A pilot study and method for central taste activation as assessed by event-related fMRI. J Neurosci Methods 131:99–105.
34. Frank GK, Reynolds JR, Shott ME, Jappe L, Yang TT, Tregellas JR, O'Reilly RC (2012): Anorexia nervosa and obesity are associated with opposite brain reward response. Neuropsychopharmacology 37:2031–2046.
35. DeGuzman M, Shott ME, Yang TT, Riederer J, Frank GKW (2017): Association of elevated reward prediction error response with weight gain in adolescent anorexia nervosa. Am J Psychiatry 174:557–565.
36. O'Doherty JP, Hampton A, Kim H (2007): Model-based fMRI and its application to reward learning and decision making. Ann N Y Acad Sci 1104:35–53.
37. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, *et al.* (2002): Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289.
38. O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004): Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science 304:452–454.
39. Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, *et al.* (1997): Acute effects of cocaine on human brain activity and emotion. Neuron 19:591–611.
40. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc B 57:289–300.
41. Westfall PH (2011): On using the bootstrap for multiple comparisons. J Biopharm Stat 21:1187–1205.
42. Kelley AE, Schochet T, Landry CF (2004): Risk taking and novelty seeking in adolescence: Introduction to part I. Ann N Y Acad Sci 1021:27–32.
43. Gusnard DA, Ollinger JM, Shulman GL, Cloninger CR, Price JL, Van Essen DC, Raichle ME (2003): Persistence and brain circuitry. Proc Natl Acad Sci U S A 100:3479–3484.
44. Atiye M, Miettunen J, Raevuori-Helkamaa A (2015): A meta-analysis of temperament in eating disorders. Eur Eat Disord Rev 23:89–99.
45. Rosenström T, Jylhä P, Robert Cloninger C, Hintsanen M, Elovainio M, Mantere O, *et al.* (2014): Temperament and character traits predict future burden of depression. J Affect Disord 158:139–147.
46. Hansenne M, Bianchi J (2009): Emotional intelligence and personality in major depression: Trait versus state effects. Psychiatry Res 166:63–68.
47. Jakšić N, Aukst-Margetić B, Marčinko D, Brajković L, Lončar M, Jakovljević M (2015): Temperament, character, and suicidality among Croatian war veterans with posttraumatic stress disorder. Psychiatr Danub 27:60–63.
48. Guyer AE, Benson B, Choate VR, Bar-Haim Y, Perez-Edgar K, Jarcho JM, *et al.* (2014): Lasting associations between early-childhood temperament and late-adolescent reward-circuitry response to peer feedback. Dev Psychopathol 26:229–243.
49. Schultz W (2004): Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. Curr Opin Neurobiol 14:139–147.
50. Vidal-Ribas P, Benson B, Vitale AD, Keren H, Harrewijn A, Fox NA, *et al.* (2019): Bidirectional associations between stress and reward processing in children and adolescents: A longitudinal neuroimaging study. Biol Psychiatry Cogn Neurosci Neuroimaging 4:893–901.
51. Zald DH, Treadway MT (2017): Reward processing, neuroeconomics, and psychopathology. Annu Rev Clin Psychol 13:471–495.
52. Muscatell KA (2018): Socioeconomic influences on brain function: Implications for health. Ann N Y Acad Sci 1428:14–32.
53. Grady CL, Rieck JR, Nichol D, Rodrigue KM, Kennedy KM (2021): Influence of sample size and analytic approach on stability and interpretation of brain-behavior correlations in task-related fMRI data. Hum Brain Mapp 42:204–219.
54. Diederen KMJ, Fletcher PC (2021): Dopamine, prediction error and beyond. Neuroscientist 27:30–46.
55. Schultz W (2019): Recent advances in understanding the role of phasic dopamine activity. F1000Res 8:F1000 Faculty Rev-1680.
56. Haarsma J, Fletcher PC, Griffin JD, Taverne HJ, Ziauddeen H, Spencer TJ, *et al.* (2020): Precision weighting of cortical unsigned prediction error signals benefits learning, is mediated by dopamine, and is impaired in psychosis [published online ahead of print Jun 24]. Mol Psychiatry.
57. Roesch MR, Calu DJ, Esber GR, Schoenbaum G (2010): All that glitters ... dissociating attention and outcome expectancy from prediction errors signals. J Neurophysiol 104:587–595.