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Research paper

Reward-circuit biomarkers of risk and resilience in adolescent depression

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ABSTRACT

Background: Dysfunctional reward processing is a core feature of major depressive disorder. While there is growing knowledge of reward processing in adolescent depression, researchers have ignored neural mechanisms of resilience to depression. Here, we examine neural correlates of reward processing that characterize resilience and risk in adolescents at risk for depression, facilitating the development of effective intervention approaches that strengthen resilience to psychopathology in at-risk youth.

Methods: 50 adolescent females were followed through age 18: 32 at-risk adolescents who either did (remitted-depressed; $n = 15$) or did not (resilient; $n = 17$) experience a depressive episode, and 18 low-risk healthy controls. Participants completed clinical assessments at 18-month intervals and an fMRI reward-processing task in late adolescence. We conducted predictive modeling with *a priori* reward regions of interest (ROIs).

Results: At-risk resilient and remitted-depressed adolescents exhibited less striatal activation than did controls during anticipation of reward. Resilient adolescents exhibited greater activation than did remitted-depressed adolescents in the middle frontal gyrus during reward anticipation, and less activation in the superior frontal gyrus and cuneus during processing of reward outcome. Using predictive modeling, ventral anterior cingulate cortex and putamen activation during reward processing distinguished resilient from remitted-depressed adolescents with 83% accuracy.

Limitations: The relatively small sample size of only females and the fact that fMRI data were obtained at one time point in late adolescence are limitations.

Conclusions: Distinct patterns of neural activation in reward circuitry appear to be markers of risk and resilience that may be targets for prevention and treatment approaches aimed at strengthening adaptive reward processing in at-risk adolescents.

1. Introduction

Major Depressive Disorder (MDD) in adolescence is associated with elevated morbidity and mortality, and is a major risk factor for suicide, a leading cause of death in this age group (Hawton and van Heeringen, 2009; Thapar et al., 2012). Adolescent-onset depression is more likely than is later-onset MDD to be recurrent and severe, and to result in long-term disability (Andersen and Teicher, 2008; Zisook et al., 2007). Females in the United States have an estimated 36% cumulative incidence of MDD during adolescence, compared to 13.6% for males (Breslau et al., 2017); in this context, adolescent females with a family history of depression are at particularly high risk for developing MDD.

Dysfunctional reward processing has been posited to underlie core features of depression, including anhedonia, depressed mood, and decreased motivation (Andersen and Teicher, 2008; Keren et al., 2018; Luking et al., 2016b; Stringaris et al., 2015). The reward circuit in the brain is a network of distributed regions involved in reward processing, including reward anticipation (i.e., 'wanting'), receipt of reward outcome (i.e., 'liking'), and, more broadly, processing of positively and negatively valenced experiences. The striatum plays a critical role in reward learning and hedonic selection of goal-directed behaviors (Liljeholm and O'Doherty, 2012). A meta-analysis examining neural correlates of reward processing in depression has documented that depressed individuals have blunted striatal response in anticipation and

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receipt of rewards (Zhang et al., 2013). Indeed, blunting of striatal response during reward processing in depressed adolescents and in adolescents at elevated risk for MDD is one of the most consistent findings in studies of reward circuitry (Gotlib et al., 2010; Luking et al., 2016a; McCabe et al., 2012; Olino et al., 2014; Stringaris et al., 2015). For example, Stringaris and colleagues examined reward processing using a monetary incentive functional magenetic resonance imaging (fMRI) task in a large community-based sample of 1576 adolescents. They found that adolescents with subthreshold depressive symptoms and those who met criteria for MDD showed reduced striatal activity during anticipation of reward relative to healthy controls (Stringaris et al., 2015). Our group and others have demonstrated that adolescents at familial risk for MDD exhibit blunted striatal activation during anticipation and receipt of reward relative to their low-risk peers (Gotlib et al., 2010; Luking et al., 2016a; Olino et al., 2014). Remitted-depressed adolescents have similarly been found to have decreased striatal responses to reward outcome (e.g., the taste of chocolate) (McCabe et al., 2012).

In addition to striatal blunting during reward processing, adolescents at risk for depression exhibit anomalous patterns of activation in cortical regions of the reward circuit, particularly in the anterior cingulate cortex (ACC) and anterior insula (Gotlib et al., 2010; McCabe et al., 2012; Olino et al., 2014). Relative to healthy controls, adolescents at familial risk for depression show reduced activation in the left insula and increased activation in the right insula in anticipation of monetary reward, and reduced activation in the ventral and dorsal ACC in response to reward outcome (Gotlib et al., 2010). Adolescents at familial risk for depression also showed less activation to taste reward (chocolate) in the ventral striatum, ventral and dorsal ACC, and orbitofrontal cortex relative to healthy controls (McCabe et al., 2012). Using a reward task involving candy, Luking and colleagues found reduced activation to reward outcome in the anterior insula and dorsal striatum in children at familial risk for depression (Luking et al., 2016a).

While multiple neuroimaging studies have examined aberrant reward processing in depressed adolescents and in adolescents at elevated risk for developing MDD, research has ignored the study of adaptive or compensatory reward processing that may underlie resilience to depression in at-risk youth. In the present study we examined neural correlates of reward processing in adolescents at risk for depression, some of whom did not develop MDD by age 18 (resilient) and others of whom experienced at least one major depressive episode by age 18 but were currently in remission (remitted-depressed), relative to low-risk healthy control adolescents. Using a fMRI-based monetary incentive reward task validated in adolescents, we compared patterns of reward circuitry activation in at-risk versus low-risk adolescents, as well as in resilient versus remitted-depressed and control adolescents. We hypothesized that, compared to controls, at-risk adolescents would show blunted striatal activation during reward anticipation and outcome (Gotlib et al., 2010; Luking et al., 2016a; Olino et al., 2014), and that resilient adolescents would show greater striatal activation during anticipation and receipt of reward than would their remitted-depressed peers. We also predicted that, compared to remitted-depressed adolescents, resilient adolescents would show greater activation in frontal cortical regions implicated in reward valuation and appraisal, reflecting an adaptive compensatory change in reward processing. Finally, no studies to date have examined the predictive value of differential patterns of activation in brain reward circuitry that confer resilience in at-risk youth. Predictive modeling has advantages over more commonly used methods that are susceptible to over-fitting; while other fit statistics can only be improved as more variables are added to a model, model prediction metrics decrease – and can even become negative – as models become over-fit. Therefore, predictive modeling should yield a more accurate representation of important indicators of resilience in at-risk youth, with potentially important clinical implications. In this context, we examined whether predictive modeling of reward circuit activation in *a priori* regions of interest would distinguish resilient from remitted-depressed at-risk adolescents. By examining patterns of activation in reward circuitry in at-risk adolescents, we begin to delineate the neurobiological underpinnings of risk for and resilience to adolescent depression and provide a foundation for understanding how to promote resilience in at-risk youth. Findings from this study have the potential to identify important neuroimaging biomarkers of risk and resilience and inform the development of more effective screening and intervention approaches for adolescents at risk for depression.

2. Methods

2.1. Participants

One-hundred and ninety female adolescents were recruited as part of a longitudinal study at Stanford University designed to examine the intergenerational transmission of risk for depression. Half of the participants were at familial risk for depression because they had a mother who had recurrent MDD episodes during the daughter's lifetime (at-risk); the other half had no personal or family history of psychopathology (low-risk healthy controls). At the time of entry into the study, participants were 9–15 years of age and had no current or lifetime history of any Axis I disorder. They were followed longitudinally throughout adolescence (for 7.61 ± 2.42 years) and completed clinical and behavioral assessments at 18-month intervals. Toward the end of adolescence (M = 18.61 ± 2.70 years), approximately five years after entering the study (M = 5.35 ± 1.79 years), 103 of the participants (49 at-risk and 54 low-risk adolescents) completed an fMRI-based reward processing task (Forbes et al., 2009). Thirty participants (19 controls, 3 resilient, and 8 remitted-depressed) were excluded because they completed the reward-processing task on a 1.5-Tesla GE whole body scanner (the remainder of the sample completed the task on a 3-Tesla scanner). An additional eight participants (4 controls, 1 resilient, and 3 remitted-depressed) were excluded because they had unusable fMRI data (e.g., excessive motion, image artifact, not responding during the task, and task malfunction). Finally, 15 participants were excluded because although they were low risk, they ultimately met DSM-IV-TR criteria for MDD or another Axis I disorder (5 controls) or did not complete follow-ups through the age of 18 years (8 controls and 2 at-risk). We report here on 50 adolescents: 17 at-risk adolescents who did not develop MDD (resilient); 15 at-risk adolescents who developed MDD after entry to the study but who were recovered by the time of the scan (remitted-depressed); and 18 low-risk adolescents who did not develop an Axis I disorder. A more detailed description of sample selection is presented in the Study Supplement.

2.2. Clinical and behavioral assessments

At each 18-month session, interviewers assessed psychopathology by administering the Kiddie Schedule for Affective Disorders and Schizophrenia present and lifetime version (K-SADS-PL Kaufman et al., 1997) or the Structured Clinical Interview for DSM (SCID; First et al., 2002) to participants who were younger or older than 18 years, respectively. Participants completed the Children's Depression Inventory – Short Form (CDI; Kovacs, 1992) to measure depressive symptomatology at the scan session.

2.3. fMRI data acquisition

Functional MRI data were acquired using a 3T MR750 Discovery scanner (GE Medical Systems, Milwaukee, WI) with a 32-channel head coil (Nova Medical). T1-weighted whole-brain anatomical images were acquired using a 5-minute GE 3D BRAVO sequence, with an IR-prep fast spoiled gradient (SPGR) sequence with 0.9 mm^3 voxel resolution (186 slices, FOV = 230 mm, TR = 6.2 ms, TE = 2.3 ms, TI = 450 ms, flip angle = 12°, 256 × 256 mm matrix, sagittal acquisition) (Forbes et al.,

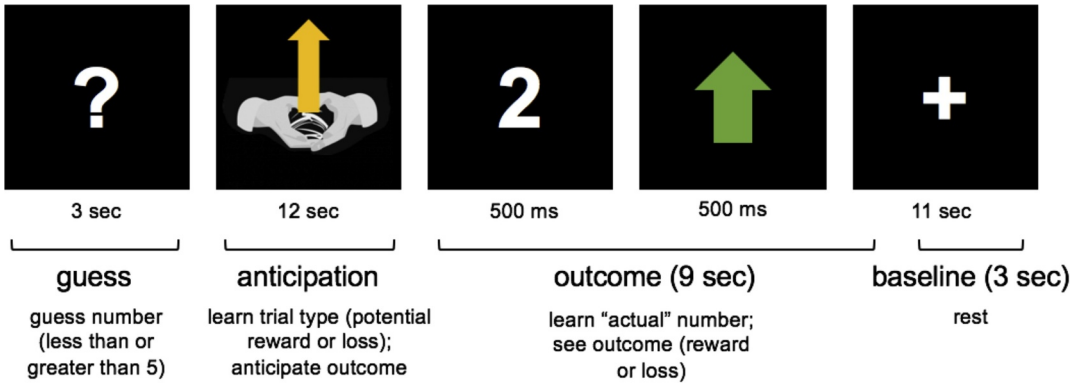

Fig. 1. Schematic of adolescent reward processing task. Participants were asked to guess the value of a number, using a button press to indicate whether it was less than or greater than 5. Next, participants learned the trial type: in reward trials, they had the potential to win points if they were correct; in the loss trials, they had the potential to lose points if they were incorrect. Finally, participants learned the outcome of the trial, which was predetermined to ensure that all participants received rewards, losses, or neutral outcomes during the same trials. An 11 s resting period followed each trial.

2009). The fMRI data were acquired with a T2*-weighted interleaved echo planar imaging sequence designed to measure whole brain BOLD contrast with 3.2mm^3 voxel resolution (37 slices, FOV = 224 mm, TR = 2000 ms, TE = 30 ms, flip angle = 77°, 165 volumes, axial acquisition with right-to-left frequency direction).

2.4. Reward processing task

Participants completed an event-related monetary incentive reward task in the scanner (Forbes et al., 2009); Fig. 1. During each trial, participants anticipated monetary reward or loss, and received feedback about the outcome of the trial (reward, loss, or neutral). Our main contrasts of interest were anticipation and outcome of reward > loss. This allowed us to probe reward circuitry while controlling for the possibility that results could be driven by group differences in baseline activation, given evidence for resilience-related differences in resting-state functional connectivity (Fischer et al., 2018). For completeness, we also report on anticipation and outcome of reward > baseline, as well as anticipation and outcome of loss > baseline in the Study Supplement.

2.5. fMRI data analysis

Analyses were conducted in FSL Version 6.0 using FEAT (FMRI Expert Analysis Tool), following standard procedures. The first four volumes of each participant's functional scan were discarded to allow for stabilization of longitudinal magnetization. The remaining images were aligned to the mean image using MCFLIRT motion correction (Jenkinson et al., 2002), and underwent spatial smoothing with a Gaussian kernel of FWHM 5 mm and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 45.0 s). Participants with more than 20 TRs of excessive motion (defined as having a framewise displacement > 0.09 mm) were excluded from all subsequent analyses (n = 1). Functional data were aligned to the structural image using the boundary-based registration algorithm (Greve and Fischl, 2009). Structural images were first aligned to standard space using FLIRT (Jenkinson et al., 2002), which was then further refined using FNIRT nonlinear registration (Andersson et al., 2007).

A voxel-wise GLM was conducted for each participant using FEAT. Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). Each condition (guess, anticipation of reward, anticipation of loss, outcome of reward, outcome of loss, and baseline) was included as a regressor of interest; regressors of non-interest included age, CDI score, and 12 motion parameters (3 translational, 3 rotational, and their derivatives), and a binary regressor indicating which TR contained excessive motion. Although none of the participants were depressed, CDI was included as a covariate to ensure that neural differences were not driven by group differences in depressive symptoms. The first and second run were combined in a fixed effects model, and group-level analysis was carried out using FLAME (Woolrich, 2008). Whole-brain Z statistic maps were thresholded using voxelwise significance determined by Z > 2.3 and a corrected cluster significance threshold of p < 0.05 (Worsley, 2001).

2.6. ROI selection

The ventral ACC (vACC), dorsal ACC, anterior insula, putamen, and ventral striatum *a priori* regions of interest (ROIs) were selected based on peak coordinates from the literature for regions known to be activated in at-risk adolescents during reward processing (Forbes et al., 2009; Oldham et al., 2018; Silverman et al., 2015). 5 mm spheres were created for each ROI, and parameter estimates were extracted from reward > loss contrasts. Visual inspection of ROI spheres indicated substantial overlap between striatal ROIs, with ventral striatum encompassing ventral putamen. Thus, the putamen, but not the ventral striatum, was included in further analyses due to its more precise anatomical definition and its importance in risk for adolescent depression documented in previous studies (Colich et al., 2017; Gotlib et al., 2010).

2.7. Predictive models

To test whether patterns of reward-related neural activation predict resilience in at-risk adolescents, logistic regression modeling was performed using ROI parameter estimates during reward anticipation and outcome (reward > loss contrasts) in the at-risk adolescents. Analyses were conducted using the caret package in R (version 6.0–78; https://CRAN.R-project.org/package=caret). To limit the number of analyses and the potential for overfitting with a small sample, we *a priori* randomly split the at-risk participants into a training (n = 20) and a validation (n = 12) set, based on standard recommendations (Hastie et al., 2009; Raamana, 2018). We conducted a series of logistic regressions on the training set using Leave-One-Out Cross-Validation, which separates a single data point (i.e., participant) to be used for testing and uses the remaining sample to estimate a prediction for the testing data point. We repeated this process for each data point in order to generate a conservative estimate of the model's predictive accuracy (Beleites and Salzer, 2008; see Supplement for more information). For the model with the highest cross-validated accuracy in the training set, we tested its ability to predict history of depression status in the at-risk adolescents in the separate, validation set.

Table 1
Participant demographic, clinical, and behavioral characteristics.

	Control (n = 18)	Remitted-depressed (n = 15)	Resilient (n = 17)	
Age at scan (years)	19.09 (2.93)	17.87 (2.68)	18.74 (2.47)	$F(2,47) = 0.86$, $p = 0.429$
Annual household income (thousands)*	87.5 (15.99)	62.27 (33.75)	76.41 (31.01)	$F(2,36) = 2.30$, $p = 0.115$
Race				$X^2(6) = 5.18$, $p = 0.520$
Caucasian	11	10	10	
African American	1	0	1	
Latin American	0	0	2	
Asian American	0	0	0	
Other/Multiracial	6	5	4	
CDI score	0.39 (0.98)	3.20 (3.71)	1.25 (1.98)	$F(2,47) = 5.76$, $p = 0.006$
Task accuracy (button presses)	23.39 (0.78)	23.80 (0.56)	23.29 (1.76)	$F(2,47) = 0.83$, $p = 0.441$
Task reaction time (milliseconds)	830.54 (202.97)	889.48 (315.50)	889.72 (358.34)	$F(2,47) = 0.23$, $p = 0.797$
Motion (absolute displacement, mm)	0.14 (0.09)	0.23 (0.28)	0.12 (0.08)	$F(2,47) = 1.83$, $p = 0.171$
Motion (relative displacement, mm)	0.03 (0.01)	0.05 (0.03)	0.04 (0.02)	$F(2,47) = 3.20$, $p = 0.050$

Means (standard deviation) displayed for low-risk controls, remitted-depressed, and resilient adolescents.
* Income was calculated by taking the median of each income bin; 11 participants declined to state and were excluded from this analysis.

2.8. Data analysis

Whole-brain maps were thresholded as described above and compared to examine group differences in reward processing. We first examined differences between the low-risk and at-risk groups as a test of general markers of familial risk. Next, within the at-risk group, we compared activation between the resilient and remitted-depressed adolescents. Finally, we assessed potential compensatory processing associated with resilience in adolescents at familial risk for MDD by examining differences between the resilient and the low-risk adolescents. For subsequent analyses, parameter estimates from selected ROIs were extracted from each participant's whole-brain map. Predictive models tested whether the resilient and remitted-depressed groups were distinguishable on the basis of reward-related activation in these ROIs.

3. Results

3.1. Participant characteristics

Participant demographic and clinical characteristics are presented in Table 1. The groups did not differ in age, income, or ethnicity. Participants had high task accuracy overall (M = 23.48 out of 24 guesses; accuracy predetermined by the task) and did not differ significantly in reaction time. The three groups differed in severity of depressive symptoms ($F(2,47) = 5.76$, $p = 0.006$). Post-hoc Tukey tests revealed that the remitted-depressed group had higher CDI scores than did the low-risk control group (95% CIs [0.78, 4.85], $p = 0.005$) but not the resilient group (95% CIs [−4.01, 0.11], $p = 0.067$); consequently, we included CDI scores as a covariate in all subsequent analyses. While the groups did not differ significantly in relative head displacement ($F(2,47) = 3.20$, $p = 0.050$), post-hoc Tukey tests revealed that the remitted-depressed group moved significantly more than did the low-risk group (95% CIs [0.00, 0.34], $p = 0.04$), which was attributable to one outlier in the remitted-depressed group. When that individual was removed from analyses, there were no group differences in absolute or relative displacement ($ps > 0.10$); results from whole-brain analyses were similar when this individual was removed (see Supplement).

3.2. Between-Group whole brain contrasts

Results of the whole-brain analyses are presented in Table 2. During anticipation of reward > loss, at-risk adolescents had less activation in left putamen and right angular gyrus than did low-risk controls (Fig. 2A). Within the at-risk group, resilient adolescents had greater activation than did remitted-depressed adolescents in the middle frontal gyrus (Fig. 2B). During outcome of reward > loss, at-risk adolescents had less activation in the precentral gyrus than did controls (Fig. 2C). Within the at-risk group, remitted-depressed adolescents had greater activation than did resilient adolescents in the cuneus and the superior frontal gyrus (SFG; Fig. 2D). Additional contrasts are reported in the Supplement.

3.3. Predictive models

The most accurate model for differentiating resilient from remitted-depressed adolescents within the at-risk group during anticipation of reward > loss included vACC and bilateral putamen (65% cross-validated accuracy in training set) (Fig. 3). When we applied this model to the testing set, it predicted resilience in the testing set above chance ($k = 0.67$, $p = 0.019$). Accuracy was 83%, with 100% sensitivity and 67% specificity. Increased vACC and left putamen activation and decreased right putamen activation were associated with a higher likelihood of having experienced MDD (OR: 0.98, 0.90, and 1.09, respectively), although none of these differences reached statistical significance (95% CIs include 1).

For outcome of reward > loss, none of the models reached cross-validated accuracy above 50% on the training set. Thus, we did not conduct these analyses on the testing set.

4. Discussion

Adolescence is a critical window of neurodevelopmental plasticity during which individuals are vulnerable to depression; however, this period also provides the opportunity for enhancing resilience to psychopathology. There is a large literature examining risk and vulnerability for depression; few studies, however, have examined neural markers of resilience to adolescent depression. In the present study we examined differential patterns of reward processing in at-risk resilient and remitted-depressed adolescents compared to low-risk healthy controls. We found that during anticipation of reward, at-risk adolescents had blunted striatal activation relative to low-risk control subjects. Within the at-risk group, resilient adolescents had greater frontal cortical activation than did remitted-depressed adolescents during anticipation of reward, and less activation in the SFG and cuneus during outcome of reward processing. Furthermore, we demonstrated that patterns of activation in *a priori* ROIs involved in reward processing can be used to predict with over 80% accuracy whether at-risk adolescents are resilient or had experienced an episode of MDD.

The finding that both resilient and remitted-depressed at-risk adolescents had blunted striatal reward response in anticipation of reward relative to their low-risk control peers is consistent with the formulation that attenuated reward response is a trait marker of risk for depression (Gotlib et al., 2010; Luking et al., 2016a; McCabe et al., 2012). In contrast to our hypothesis, resilient adolescents did not show greater

Table 2
Whole-brain between-group differences in processing of reward > loss.

	Peak coordinates (MNI)				
	x	y	z	Z-value	Cluster extent
Anticipation of reward > loss					
Control > At-risk					
Left putamen	−30	12	6	3.32	567
Right angular gyrus	58	−60	30	3.68	823
Resilient > Depressed					
Middle frontal gyrus	32	4	56	4.48	723
Outcome of reward > loss					
Control > At-risk					
Precentral gyrus	−28	−30	60	3.43	615
Depressed > Resilient					
Superior frontal gyrus	−24	42	38	4.19	620
Cuneus	−18	−90	20	3.27	642

Significant between-group differences for low-risk healthy controls and at-risk remitted-depressed and resilient adolescents. Coordinates are in Montreal Neurological Institute (MNI) space. Whole-brain z maps were thresholded using voxelwise significance of $Z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$.

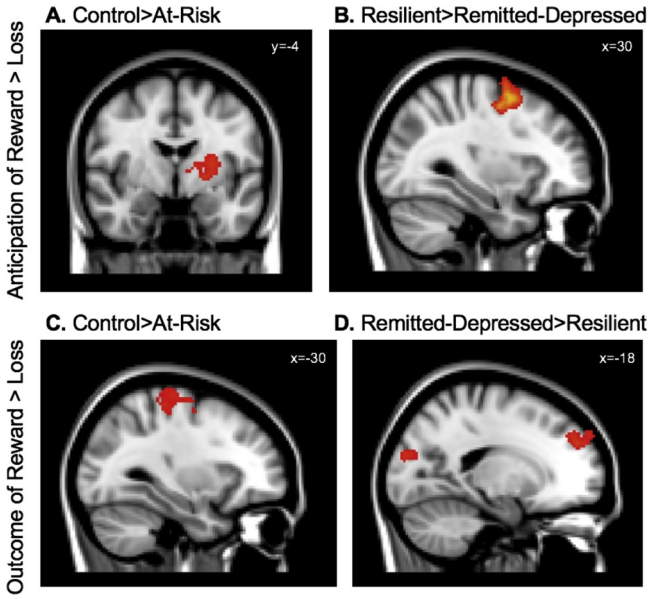

Fig. 2. Significant between-group differences during anticipation and outcome of reward > loss. A) Low-risk healthy controls show greater putamen activation than do at-risk remitted-depressed and resilient adolescents. B) At-risk resilient adolescents show greater middle frontal gyrus activation than do remitted-depressed adolescents. Significant group differences during outcome of reward > loss: C) low-risk adolescents show greater activation in the precentral gyrus than do at-risk resilient and remitted-depressed adolescents. D) At-risk remitted-depressed adolescents show greater activation than do resilient adolescents in the superior frontal gyrus and cuneus.

striatal activation than did remitted-depressed adolescents; both had significantly blunted striatal activation in anticipation of reward relative to healthy low-risk controls. This finding suggests that resilient adolescents develop adaptive compensatory processes to remain healthy despite blunted striatal activation. The results of this study help to answer unresolved questions concerning reward circuitry in at-risk youth (Luking et al., 2016b), and suggest that 'normative' reward activation in striatal regions does not appear to be a prerequisite for resilience in at-risk offspring.

Relative to remitted-depressed adolescents, resilient subjects had greater activation in the middle frontal gyrus during anticipation of reward. This region has been implicated in cognitive control functions such as selective attention and executive functioning (Aron et al., 2003), as well as in goal-directed action-selection and reward-based association learning (Ridderinkhof et al., 2004). This region of the lateral prefrontal cortex is posited to be responsible for maintaining anticipatory reward outcome representations in an active state until the goal is achieved, often in the face of other intervening and potentially interfering events (Miller and Cohen, 2001). This may allow resilient adolescents, compared to their at-risk peers who developed depression, to have greater 'top-down' executive control and optimize decision making processes underlying goal-directed action selection that serve compensatory functions to allow for more adaptive cognitive reappraisal and attentional modulation of motivationally salient stimuli (Bermpohl et al., 2009; Erk et al., 2010).

In contrast to our hypothesis, we found no significant differences in striatal activation among resilient, remitted-depressed, and low-risk control adolescents in the processing of reward outcome. In fact, the literature is mixed: whereas some studies have found blunting of striatal response only during anticipation of reward, others have found striatal blunting during reward outcome (Oldham et al., 2018; Silverman et al., 2015). Remitted-depressed adolescents did have greater activation than did resilient adolescents in the cuneus during processing of reward outcome, a region implicated in selective attention processing in visuomotor networks (Vanni et al., 2001) and in inhibition of motor response (Matthews et al., 2005). They also had greater SFG activation during processing of reward outcome relative to their resilient peers. The SFG is posited to contribute to higher cognitive functions, particularly to working memory with respect to spatial cognition (du Boisgueheneuc et al., 2006). Although their respective roles in reward processing have yet to be delineated, a recent meta-analysis implicates increased cuneus and SFG activity in depression during reward processing (Zhang et al., 2013), suggesting that involvement of these brain regions that have not been traditionally considered part of reward circuitry are important components of reward processing in depression that may be involved in reward expectation in response to visual stimuli. In this context, our findings suggest that aberrant patterns of activation in brain regions implicated in visuo-motor selective attention processing of rewarding stimuli are important in distinguishing at-risk resilient from remitted-depressed adolescents.

Using predictive modeling of patterns of activation in anticipation of reward within *a priori* ROIs implicated in adolescent depression and reward processing – the vACC and bilateral dorsal striatum – we were able to distinguish resilient from remitted-depressed at-risk adolescents with greater than 80% accuracy. Indeed, activation patterns within fronto-striatal regions of reward circuitry are considered to be important psychophysiological markers of depression (Dunlop and Nemeroff, 2007; Hasler et al., 2004). Previous work has demonstrated that depressed adolescents show reduced fronto-striatal activity during processing of reward anticipation (Olino et al., 2014; Stringaris et al.,

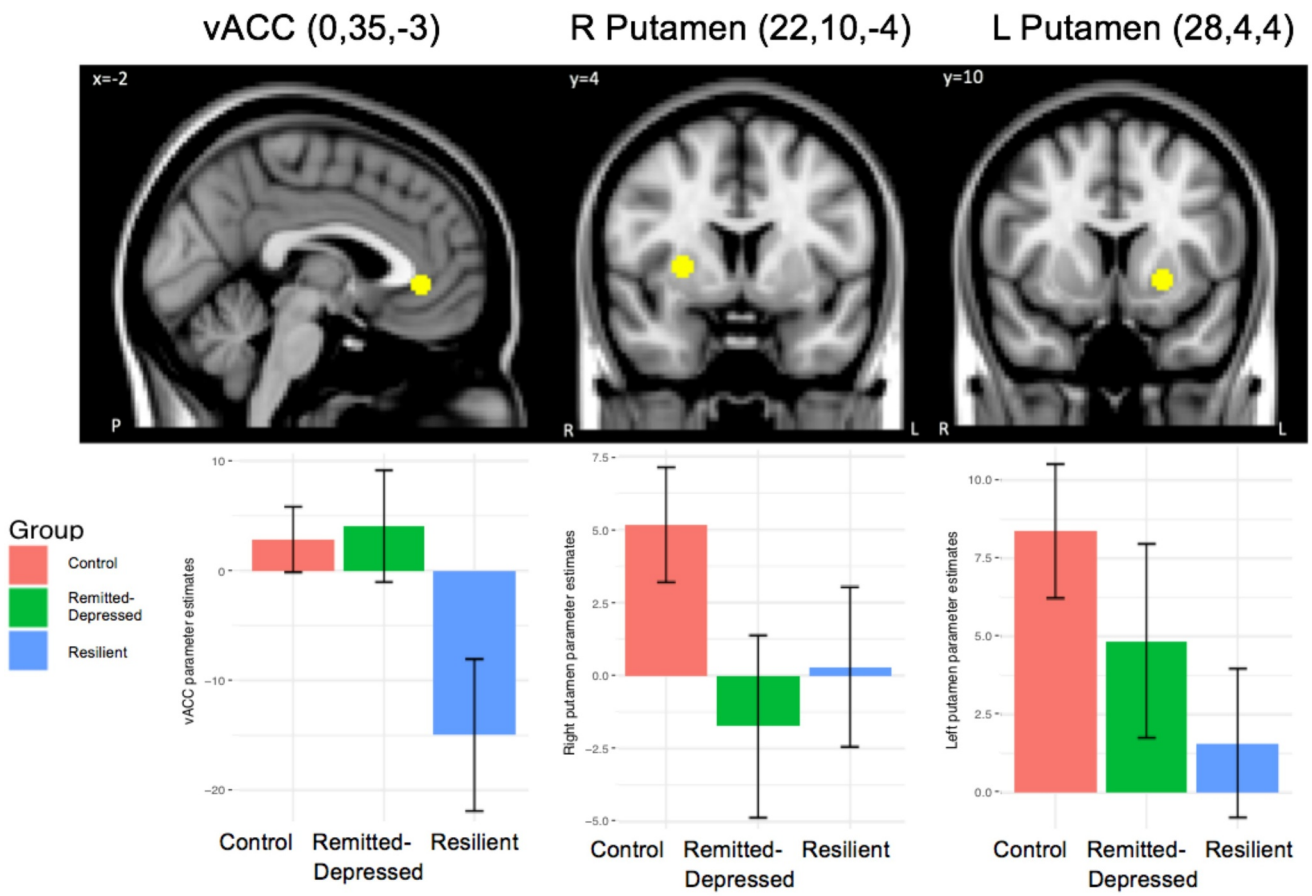

Fig. 3. Predictive modeling of reward processing in at-risk adolescent females. At-risk resilient adolescents (RES) showed less activation of the ventral anterior cingulate cortex (vACC) during anticipation of reward > loss than did at-risk remitted-depressed and low-risk healthy control adolescents. Low-risk adolescents also showed more activation of right and left putamen than did at-risk resilient and at-risk remitted-depressed adolescents. Coordinates in MNI (Montreal Neurological Institute) space.

2015) and reward outcome (Gotlib et al., 2010; Luking et al., 2016a). Remitted-depressed and never-depressed youth at familial risk for MDD similarly show hypoactivation within the anterior cingulate cortex and striatum in anticipation of reward, relative to healthy controls (McCabe et al., 2009; McCabe et al., 2012). The present study is the first, however, to attempt to apply these putative reward-based neuroimaging biomarkers to predictive modeling of risk and resilience in at-risk adolescents. Although our findings must be replicated prospectively in a larger sample, vACC and putamen activation in response to reward versus loss appears to differentially predict resilience versus experiencing MDD in at-risk adolescents and, therefore, may be a reward-circuit biomarker that would allow for early identification and intervention approaches for adolescents at risk for depression. This analysis improves on more commonly used modeling methods, allowing for a more sensitive measure of group differences that is less susceptible to overfitting.

While additional prospective research is required to validate our study findings in larger samples, the unique reward-circuit biomarkers of risk and resilience identified in this study have important clinically translatable implications. Distinct patterns of neural activation in the processing of reward may not only allow us to identify neuroimaging markers that differentiate resilience and risk to depression in at-risk adolescents, but may also assist in the development of more effective prevention and intervention approaches aimed at strengthening adaptive reward processing in at-risk youth. For example, instead of attempting to augment, and thereby normalize, blunted striatal activation – a pattern that also characterizes resilient adolescents – identifying neural markers of resilience will facilitate the development of cognitive-behavioral, psychopharmacologic, or neuromodulatory interventions aimed at strengthening neural circuit projections that enhance healthy adaptive functioning in adolescents at risk for depression. More broadly, by shifting the focus of research to incorporate a resilience-based approach, we can identify characteristics of at-risk individuals who have learned to cope adaptively despite experiencing adversity. This will allow us to utilize a strength-based focus with current pathology-based models and treatment approaches, and to develop diagnostic and therapeutic targets that optimize resilience.

We should note four limitations of this study. First, although we assessed clinical and behavioral measures longitudinally over the course of adolescence, the fMRI data reported in this study were obtained at one time point, late in adolescence. Future studies with neuroimaging scans conducted over the course of adolescence are needed to examine developmental alterations in reward processing that promote and predict resilience and the onset of depression in at-risk youth. Second, the relatively small sample size is a limitation of this study; future investigations with larger samples are needed to replicate and extend our findings, particularly with respect to validating findings of our predictive model. Third, we used MDD history in the mothers to define risk groups. History of MDD in fathers and other extended family members, as well as other mental illness, also increase risk for depression (Wilde et al., 2014); thus, future studies should include a detailed family history of psychopathology. Finally, the present study assessed adolescent females, given their higher risk for depression; future studies should examine reward processing differences in at-risk males to determine whether comparable findings are obtained.

In conclusion, findings of this study advance our understanding of

the neural basis of reward processing that may not only confer vulnerability, but also promote resilience in adolescents at risk for depression. Resilient youth appear to show adaptive compensatory changes despite blunting of striatal activation in anticipation of reward, indicating that reward processing in at-risk resilient adolescents is not equivalent to that of low-risk controls, or simply the absence of 'dysfunction' within brain networks. By continuing to examine the neural basis of resilience in at-risk populations, we will not only elucidate the neurobiological mechanisms of resilience, but will also help provide a foundation for understanding how to promote resilience in at-risk youth and inform the development of more effective screening and early intervention approaches.

Author disclosure

The study was approved by the Institutional Review Board at Stanford University; written assent or consent was obtained from all study participants and written consent was obtained from their parents.

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Disclosures

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.12.104.

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