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# Like mother like daughter: putamen activation as a mechanism underlying intergenerational risk for depression

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## Abstract

Having a depressed mother is one of the strongest predictors for developing depression in adolescence. Given the role of aberrant reward processing in the onset and maintenance of depression, we examined the association between mothers' and their daughters' neural response to the anticipation of reward and loss. Fifteen non-depressed mothers with a history of recurrent depression and their never-disordered daughters, and 23 mothers without past or current depression and their never-disordered daughters, underwent functional magnetic resonance imaging while performing the monetary incentive delay task. To assess mother-daughter concordance, we first identified ROIs involved in the anticipation of reward and loss across all mother-daughter pairs. Within each of these ROIs, we examined the association between mothers' and daughters' neural response, and the interaction between group status and mothers' neural response in predicting daughters' neural response. We found a significant association between mothers' and daughters' putamen response to the anticipation of loss, regardless of mother's depression history. Furthermore, pubertal stage moderated the association between mother-daughter putamen concordance. Our findings suggest a unique role of the putamen in the maternal transmission of reward learning and have important implications for understanding disorders characterized by disturbances in reward learning and processing, such as major depression.

**Key words:** depression; concordance; putamen; fMRI; reward; loss

## Introduction

Having a depressed parent is one of the strongest predictors for developing depression in adolescence and early adulthood; indeed, offspring of a depressed parent have a 3- to 5-fold increased risk of developing depression or a related form of psychopathology (Colich *et al.*, 2015; Gotlib and Colich, 2014). Researchers have documented the negative consequences of parental depression for offspring, even prior to the experience of a depressive episode themselves (Halligan *et al.*, 2007; Joormann *et al.*, 2007; Dearing and Gotlib, 2009; Chen *et al.*, 2010; Joormann *et al.*, 2010; Colich *et al.*, 2015). Given the adverse impact of parental depression, it is imperative that we gain a

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better understanding of the mechanisms underlying the intergenerational transmission of risk for this disorder. While heritability estimates for Major Depressive Disorder (MDD) range from 30–40% (see Flint and Kendler, 2014; Lau *et al.*, 2014 for a review of the genetics of depression), exposure to adverse environmental factors, including being raised by a depressed parent, are also likely to contribute to the higher risk for depression experienced by offspring of depressed parents. Thus, it is important to examine heritable endophenotypes, such as brain structure and function, that are also shaped by environmental processes.

In an effort to understand the intergenerational transmission of neural circuitry relevant to emotional processing, researchers have recently begun to examine neural concordance between parents and their offspring (Foland-Ross *et al.*, 2016; Ho *et al.*, 2016; Yamagata *et al.*, 2016). For example, Yamagata *et al.* (2016) examined patterns of regional tissue volume in corticolimbic structures in parents and their children. These investigators found that concordance in tissue volumes of mother-daughter pairs was stronger than in both father-daughter and mother-son pairs in specific corticolimbic regions, including the right amygdala, bilateral ACC, vmPFC, OFC, right hippocampus and bilateral parahippocampus gyrus. Given that aberrant corticolimbic function and structure are implicated in a number of forms of psychopathology, including mood disorders, Yamagata *et al.* posited that similarities in mother-daughter neural structure may underlie the maternal transmission of mood disorders. Consistent with this formulation, Foland-Ross *et al.* (2016) found that daughters of mothers with a history of recurrent depression, who are at high risk for developing depression themselves, exhibited patterns of cortical thinning in bilateral fusiform gyri that mirrored cortical thinning identified in their mothers. Moreover, within the high-risk group only, mothers' pattern of cortical thinning uniquely predicted daughters' cortical thinning in this region. Together, these data indicate that there is a strong pattern of maternal inheritance of neural structure that may contribute to the maternal transmission of risk for depression in their offspring. The data presented in these two studies, which differed from each other with respect to design and analyses, raise two competing models of the transmission of risk for MDD. Yamagata *et al.*'s data suggest that depression-related neural structures are similarly concordant across all mothers and their daughters; however, the authors did not explicitly assess clinical disorders in their sample and nor did they compare depressed mothers and their daughters with nondepressed mothers and their daughters. Conversely, Foland-Ross *et al.*'s findings suggest that patterns of neural structural concordance between depressed mothers and their daughters, but not between healthy mothers and daughters, contribute to the intergenerational transmission of MDD. Importantly, no studies to date have examined neural concordance between parent and offspring using measures of brain *function*, which may be linked more strongly to depression-relevant problematic cognitions and behaviors than is brain structure. Assessing maternal-offspring concordance in neural function, therefore, may also be useful in definitively testing these two potential neural models of maternal transmission of depression risk.

Although there is considerable heterogeneity in the clinical presentation of MDD, anhedonia, or loss of interest or pleasure in rewarding stimuli, represents a core symptom of the disorder. In fact, researchers have found that individuals diagnosed with MDD respond to rewarding stimuli with significantly less positive affect than do their non-depressed counterparts, particularly when *anticipating* a rewarding stimulus, suggesting that depressed individuals have anomalous reinforcement learning (McFarland and Klein, 2009; Simmons and Drevets, 2012; Huys *et al.*, 2013; Chen *et al.*, 2015). Hyporesponsive mesolimbic dopamine pathways and related brain regions in the striatum are posited to underlie anhedonia and, more generally, dysfunctional anticipatory reward processing and reinforcement learning in MDD (Nestler *et al.*, 2002; Nestler and Carlezon, 2006; Knutson *et al.*, 2008; Pizzagalli *et al.*, 2009; Pizzagalli, 2014; Robbins, 2016). It is possible, therefore, that reduced striatal response during reinforcement learning is a marker of vulnerability for the development of depression (Bress *et al.*, 2013; Morgan *et al.*, 2013; Nelson *et al.*, 2016; Luking *et al.*, 2016). As one example, abnormal development of striatal responses to reward (e.g. not showing the adolescent-typical increase in striatal response to reward) have been found to predict the subsequent onset of depressive symptoms in adolescents (Goff *et al.*, 2013; Hanson *et al.*, 2015). Similarly, several investigators have reported blunted striatal activation in individuals at familial risk for depression. For example, Gotlib *et al.* (2010) found that healthy adolescent daughters of mothers with a history of depression exhibited less activation in the striatum and left insula during anticipation of reward and loss than did daughters of never-disordered mothers. Similarly, Olino *et al.* (2014) found that, even after controlling for current depressive symptoms, offspring of depressed parents showed blunted ventral striatum and caudate response to reward anticipation–however, they did not present data from the loss anticipation condition. Finally, Sharp *et al.* (2014) found reduced striatal activity in response to reward outcome in both currently depressed girls and girls at familial risk for depression, relative to healthy controls. Again, these investigators did not present data from the loss anticipation condition. While these findings are promising in indicating a role for aberrant neural processing of reward in the risk for and diagnosis of major depression, whether striatal dysfunction–and specifically in response to losses–in youth at risk for depression in concordance with that of their depressed parents is unclear.

In this study, we build on these findings to examine the similarity, or concordance, between mothers' and daughters' patterns of functional activation, quantified by functional magnetic resonance imaging (fMRI) BOLD responses during a well-validated task assessing the anticipation of reward *and* loss (Knutson *et al.*, 2000; Knutson *et al.*, 2008). We recruited two groups of mother-daughter dyads: currently nondepressed mothers with a history of recurrent depression (remitted mothers; RMD) and their never-disordered daughters who are at familial risk for developing depression (RSK); and mothers without past or current depression (CTL) and their never-disordered daughters (CTL). Guided by prior literature demonstrating the role of aberrant reinforcement learning and reward processing in depression (Gotlib *et al.*, 2010; Goff *et al.*, 2013; Morgan *et al.*, 2013; Hanson *et al.*, 2015), we examined functional neural responses to the anticipation of reward and loss in dyads in both groups. In addition, we also examined the concordance between mothers' and daughters' neural response when preparing a motor response during the task in order to test whether effects are specific to striatal activation. Given prior literature pointing to two potential models of maternal inheritance of neural structure (Foland-Ross *et al.*, 2016; Yamagata *et al.*, 2016), it was unclear whether we should expect to find a pattern of concordance that is specific to the RMD/RSK group, or that is similar across all mothers-daughter pairs. Thus, we tested these alternatives in our analyses. We first identified regions of

interest (ROIs) by isolating regions that were active during anticipation of reward and loss across all participants. We then examined whether there was an association between mothers' neural response and their daughters' neural response in these ROIs. We predicted that there would be a significant association, or concordance, between mothers' and daughters' neural response to reward in striatal regions implicated in risk for depression, but not in motor regions implicated in preparing a motor response during the task. We then tested whether group status (RMD/RSK *vs* CTL/CTL) moderated the association between mothers' and daughters' neural response in these ROIs (as in Foland-Ross *et al*., 2016), or whether the association between mothers' and daughters' neural response was consistent across RMD/RSK and CTL dyads (as in Yamagata *et al*., 2016). Finally, we examined whether age of pubertal status moderated the association between mothers' and daughters' neural response.

## Materials and Methods

### Participants

Participants were recruited as part of a larger study of 190 mother-daughter pairs examining the intergenerational transmission of risk for depression at Stanford University. Mother-daughter pairs were recruited through local community outreach, and all interested participants completed a telephone screening interview to establish initial eligibility criteria. Individuals were excluded from the study if either mother or daughter had experienced severe head trauma or had a learning disability that might interfere with task performance. Eligible mothers and their daughters between the ages of 9 and 15 years were invited to participate in a laboratory session during which they were administered structured diagnostic interviews: the Kiddie Schedule for Affective Disorders (K-SADS-PL; Kaufman *et al*., 1997) to both daughters and their mothers (about the daughters), and the Structured Clinical Interview for DSM-IV (SCID; First *et al*., 1997) to the mothers. Interviewers for the K-SADS-PL and SCID had previous experience administering structured clinical interviews and had excellent interrater reliability ($K = 1.00$). Eligibility criteria for mother-daughter dyads included having a mother with a history of depression during their daughter's lifetime (RMD/RSK group–no mothers were currently experiencing a depressive episode), or having a mother without any past or current Axis I disorder (CTL group). Dyads were excluded if daughters met criteria for any current or past Axis I disorder (according to either mothers' or daughters' report on the K-SADS-PL). This study was approved by the institutional review board (IRB) at Stanford University. All mothers gave informed consent and daughters gave assent. For this study, we report results from the 76 participants (23 CTL mothers and 23 CTL daughters; 15 RMD mothers and 15 RSK daughters) for whom we had high-quality fMRI data from both mother and daughter on the same scanner. Six of 23 CTL daughters and 7 of 15 RSK daughters were from the sample reported on by Gotlib *et al*. (2010); however, the mothers' fMRI data have never been published and the issue of concordance has not been examined.

### Self-report measures

In addition to completing questionnaires to obtain demographic, medical and clinical information, all daughters completed the 10-item Child Depression Inventory (CDI-S; Kovacs, 1985), a self-report measure of depressive symptoms experienced in the past 2 weeks. The internal consistency for this measure in the current sample was $\alpha = 0.65$. Daughters also completed the Tanner Staging questionnaire to assess self-report pubertal status (Marshall and Tanner, 1969). Average Tanner scores for each participant were calculated by averaging Tanner pubic hair and Tanner breast development scores. Two participants did not complete the Tanner staging questionnaire. All mothers completed the Beck Depression Inventory-II (BDI-II; Beck *et al*., 1996), a 21-item self-report measure of depressive symptoms in adults. The internal consistency for this measure in the current sample was $\alpha = 0.94$.

### fMRI data acquisition

All MRI data were collected on a 1.5-Tesla GE whole-body scanner (GE Healthcare Systems, Milwaukee, Wisconsin). A T2*-sensitive gradient echo spiral in/out pulse sequence was used for functional imaging (24 axial slices, TR/TE = 2000/40 ms, flip angle = 90°, FOV = 240 mm, 64 x 64; in-plane resolution = 3.75 x 3.75 $mm^2$, 4 mm slice thickness). The total duration of the functional scan was 10 : 28. High-resolution structural images were obtained using a T1-weighted spoiled gradient-recalled (SPGR) acquisition in a steady state sequence (116 slices, TR/TE = 8.924/1.792 ms, flip angle = 15°, FOV = 22 cm, 256 x 192; in-plane resolution = 0.859 x 0.859 $mm^2$, 1.5 mm slice thickness).

### fMRI reward processing task protocol

Participants completed the KIDMID task in the scanner (for a full description of this task, see Gotlib *et al*., 2010). The KIDMID task was based on Knutson *et al*.'s (2000, 2008) adult monetary incentive delay (MID) task and was designed to probe children's neural activation to the anticipation of rewards and losses. In this task, participants respond to a target as quickly as possible in order to gain points (reward trials) or to avoid losing points (loss trials). Points accrued during the run were then converted into 3 tiers of prizes with which participants were presented prior to the scan. For example, level 1 prizes consisted of pencils, pens, nail polish, etc.; level 2 prizes consisted of picture frames, tote bags, art kits, etc.; and level 3 prizes consisted of gift cards to Starbucks, iTunes and Barnes and Noble. Briefly, the task consisted of a single run of 100 trials, each lasting 6 s. Each trial began with an anticipation phase, during which a cue was presented to signify the trial type (circle = reward trial; square = loss trial; triangle = neutral trial). Participants were then presented with the target (a star) of variable duration, and they pressed a button as quickly as possible (or, on neutral trials, did not press the button). Participants then received feedback about whether they responded quickly enough to gain points or to avoid losing points on that trial. For incentive trials (reward or loss trials), either 1 or 5 points were at stake; for neutral trials, a '0' was presented because participants could neither win nor lose points on these non-incentive trials.

More specifically, each cue type (circle, square, triangle) appeared 20 times and each trial type was pseudorandomized across the run. The cue during anticipation was presented for 250 ms and was followed by a variable interstimulus interval (ISI) for a total of 200–2500 ms. The target was presented for 250–350 ms, determined from pilot testing to yield 75% accuracy. A second variable ISI separated the offset of the target stimulus from the onset of the feedback phase that informed participants whether they had lost or won points. This second ISI was calibrated so that the length of the entire trial was

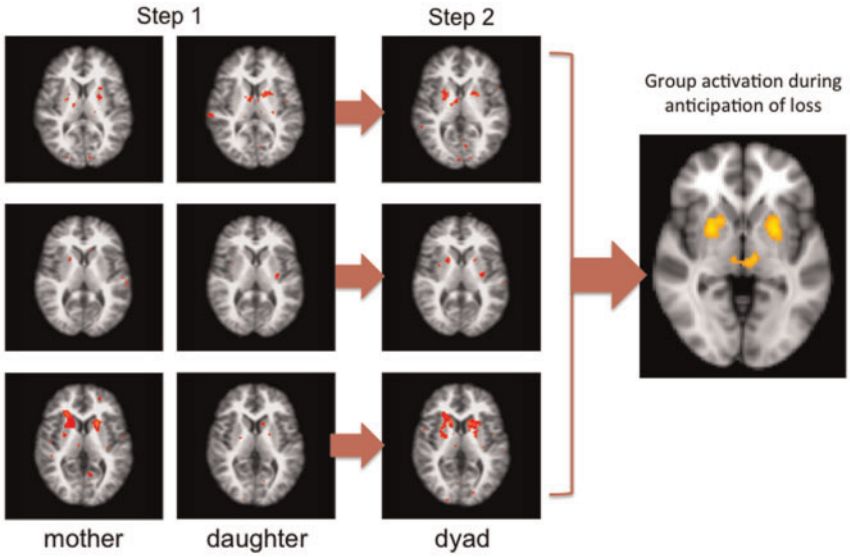


**Fig. 1.** We used a multistep analytic procedure to identify the association, or concordance, between mothers' and daughters' neural response to the anticipation of reward and loss. We first combined all participant-level data (from mothers and their daughters) into an average map for each dyad. We then combined all dyad maps to create a map of average activation for all participants for both anticipation of reward greater than neutral and anticipation of loss greater than neutral. Group Z-statistical maps for each condition (anticipation of reward and anticipation of loss) were thresholded at $Z > 3.0$ with a cluster probability of $P < 0.01$, corrected for whole-brain multiple comparisons using Gaussian random field theory. We then isolated independent clusters of activation for each contrast across all participants and extracted parameter estimates (PEs) for both anticipation of reward *vs* anticipation of neutral and anticipation of loss *vs* anticipation of neutral for each individual.

consistently 6 s. The feedback phase lasted 1650 ms. For the purpose of these analyses, we compared neural activation during anticipation in reward and loss trials to activation during anticipation in non-incentive neutral trials. Reaction time and hit rates were recorded for each trial of the KIDMID task.

***fMRI data analysis.*** Analyses were conducted in FSL Version 6.0 using FEAT (FMRI Expert Analysis Tool). The first four volumes of each participant's functional scan were discarded to allow for stabilization of longitudinal magnetization. The remaining images were preprocessed using standardized methods. Preprocessing included motion correction to the mean image (Jenkinson *et al.*, 2002), spatial smoothing (Gaussian kernel FWHM = 5 mm), and high-pass temporal filtering ($t > 0.01$ Hz; Woolrich *et al.*, 2001). Functional data were linearly registered to a common stereotaxic space by first registering to the in-plane T2 image (6 degrees of freedom) then to the MNI152 T1 2 mm brain (12 degrees of freedom; Jenkinson and Smith, 2001).

Using FEAT, a voxel-wise GLM was conducted for each participant. Each anticipation condition (anticipation of reward, anticipation of loss, and non-incentive neutral trials) was included as a regressor of interest, and the target and all outcome conditions were included as regressors of non-interest. The six motion parameters were also included as regressors of non-interest.

### ROI selection: anticipation of reward and loss *vs* neutral

We used a multistep analytic procedure to identify the association, or concordance, between mothers' and daughters' neural response to the anticipation of reward and loss (see Figure 1 for a schematic of our whole-brain analyses to select ROIs). We first combined all subject-level data (from mothers and their daughters) into a fixed effects model to account for non-independence of mother-daughter data. We then included all fixed effects models for each mother-daughter dyad in a mixed-effects group-level model using FSL's FLAME (FMRIB's Local Analysis of Mixed Effects State) stage 1 (Beckmann *et al.*, 2003; Woolrich *et al.*, 2004; Woolrich, 2008). To isolate independent ROIs and minimize the number of tests conducted, group Z-statistical maps for each condition (anticipation of reward and anticipation of loss) were thresholded at $Z > 3.0$ with a cluster probability of $P < 0.01$, corrected for whole-brain multiple comparisons using Gaussian random field theory. We then isolated independent clusters of activation for each contrast across all participants and extracted parameter estimates (PEs) for both anticipation of reward *vs* anticipation of neutral, and anticipation of loss *vs* anticipation of neutral for each individual.

### Operationalizing neural concordance

To assess mother-daughter concordance of neural response to the anticipation of reward and loss, we conducted a series of partial correlation analyses controlling for daughter's age (given evidence of age-related changes in striatal response to reward across development; Somerville *et al.*, 2010; Van Leijenhorst *et al.*, 2010) for each of the significant ROIs across both groups.

### Group differences in neural concordance

For any ROI that showed a significant association between mother and daughter across both groups, we then conducted a moderation analysis to examine whether the association between mothers' and daughters' PEs differed as a function of RSK/RMD group *vs* CTL group status. We also compared mean parameter estimates in any ROI that showed significant concordance between the RSK/RMD and CTL groups using two-sample *t*-tests.

### Developmental influences on bilateral putamen concordance

To test whether daughters' age or pubertal status (as indexed by Tanner staging) moderated the association between mothers'

**Table 1.** Participant characteristics

| Daughters | | | |
|---|---|---|---|
| | CTL ($n = 23$) | RSK ($n = 15$) | |
| Age, M (s.d.) | 13.07 (1.36) | 12.83 (1.57) | $t(36) = 0.49$, $P = 0.62$ |
| Tanner stage, M (s.d.) | 3.25 (0.86) | 3.32 (0.93) | $t(34) = -0.24$, $P = 0.82$ |
| CDI, M (s.d.) | 1.13 (1.39) | 1.80 (1.97) | $t(36) = -1.23$, $P = 0.23$ |
| Psychotropic medication | 0 | 1 | $\chi^2(1) = 7.69$, $P = 0.01$ |
| Reaction time, M (s.d.) | | | |
| Gain trials | 221.08 (20.37) | 222.30 (29.25) | $t(36) = -0.15$, $P = 0.88$ |
| Loss trials | 225.02 (20.73) | 226.92 (30.73) | $t(36) = -0.23$, $P = 0.82$ |
| Hit rates, % | | | |
| Gain trials | 90.76 | 91.5 | $t(36) = -0.39$, $P = 0.70$ |
| Loss trials | 88.8 | 90 | $t(36) = -0.53$, $P = 0.60$ |
| *Mothers* | | | |
| | CTL ($n = 23$) | RMD ($n = 15$) | |
| Age, M (s.d.) | 47.29 (3.74) | 44.31 (6.90) | $t(36) = 1.73$, $P = 0.09$ |
| BDI -II, M (s.d.) | 3.64 (4.10) | 13.53 (9.77) | $t(34) = 4.17$, $P < 0.01$ |
| Psychotropic medication | 1 | 6 | $\chi^2(1) = 0.21$, $P = 0.40$ |
| Reaction time, M (s.d.) | | | |
| Gain trials | 236.82 (64.64) | 208.14 (26.13) | $t(36) = 1.63$, $P = 0.11$ |
| Loss trials | 240.28 (63.53) | 211.02 (27.35) | $t(36) = 1.68$, $P = 0.10$ |
| Hit rates, % | | | |
| Gain trials | 89.24 | 91.67 | $t(36) = -0.82$, $P = 0.42$ |
| Loss trials | 84.89 | 89.00 | $t(36) = -0.69$, $P = 0.50$ |

**Table 2.** Neural data for anticipation of reward > neutral and anticipation of loss > neutral

| Brain region | MNI coordinates | | | Z-value | No. of voxels |
|---|---|---|---|---|---|
| | x | y | z | | |
| Anticipation of reward > Anticipation of neutral | | | | | |
| L Putamen | –24 | 4 | 6 | 5.83 | 733 |
| Supplementary motor area | –4 | 0 | 52 | 5.82 | 731 |
| R putamen | 26 | 6 | 0 | 5.27 | 663 |
| L postcentral gyrus | –38 | –18 | 52 | 5.95 | 613 |
| Bilateral thalamus | 8 | –20 | –2 | 4.28 | 419 |
| R precentral gyrus | 58 | 6 | 46 | 4.56 | 262 |
| Anticipation of loss > Anticipation of neutral | | | | | |
| L putamen | –24 | 4 | 6 | 5.58 | 491 |
| R putamen | 24 | 4 | 2 | 5.03 | 413 |
| L postcentral gyrus | –36 | –24 | 52 | 5.58 | 346 |
| Supplementary motor area | 6 | 2 | 54 | 4.86 | 250 |
| Bilateral thalamus | –8 | –20 | –4 | 4.32 | 179 |

and their daughters' bilateral putamen response to loss, we conducted moderation analyses to test the interactions of mothers' neural data and daughters' age, and mothers' neural data and daughters' pubertal status, in two independent models [due to the highly correlated nature of these two variables, $r(36) = 0.557$, $P < 0.01$]. For models that showed significant interaction effects, we performed simple slope tests to test for significance at 1 s.d. above and below the moderator.

### Correlations between neural concordance and depression symptomatology

In order to examine whether degree of concordance was related to clinical characteristics in mothers and daughters, we Z-scored parameter estimates from ROIs that showed a significant association between mother and daughter across both groups. We then subtracted daughters' scores from mothers' scores and used the absolute value of this difference as a metric reflecting the degree of similarity of mothers' and daughters' putamen response. We then correlated this value with mothers' BDI and daughters' CDI scores within the CTL and RMD/RSK groups separately using two-tailed Pearson's correlation coefficient.

## Results

### Participant characteristics

Demographic and clinical characteristics and behavioral KIDMID performance of the mothers and daughters are presented in Table 1. RSK and CTL daughters did not differ in age, pubertal status, or CDI scores. RMD and CTL mothers did not differ in age but, as expected, did differ in BDI-II scores (Table 1).

### ROI selection: anticipation of reward and loss *vs* neutral

In order to examine neural responses to the anticipation of reward and loss relative to the anticipation of neutral stimuli across all mothers and daughters, we conducted a whole brain mixed-effects model. This voxel-wise analysis yielded significant clusters for the anticipation of reward relative to the anticipation of neutral conditions in six large clusters: right precentral gyrus, thalamus, left postcentral gyrus, right putamen, left putamen and supplementary motor area (Table 2). The voxel-wise analysis for anticipation of loss relative to the anticipation of neutral contrast yielded five large clusters in the thalamus, left postcentral gyrus, right putamen, left putamen and supplementary motor area (Table 2). We then created ROIs based on each of these significant clusters and extracted PEs for both the anticipation of reward relative to neutral and anticipation of loss relative to neutral. Because we had no laterality-specific hypotheses, we combined left and right putamen ROIs to create one bilateral putamen ROI for both the anticipation of reward relative to neutral and the anticipation of loss relative to neutral conditions.

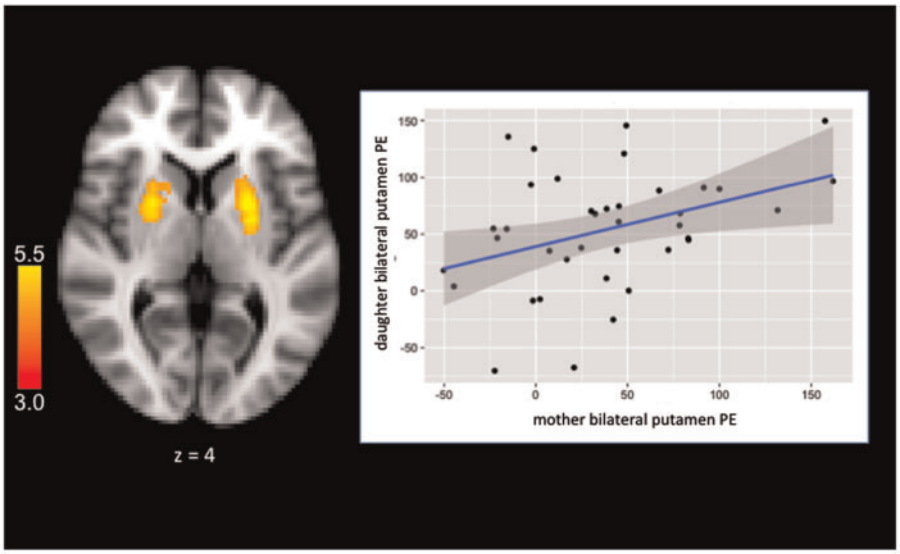


**Fig. 2.** Bilateral putamen in response to the anticipation of loss greater than anticipation of neutral was the only region to show a significant association, or concordance, between all mothers and daughters, regardless of mothers' depression history. Activation map is thresholded at $Z > 3.0$ and corrected for multiple comparisons using a cluster-based $P < 0.01$. MNI coordinates are indicated for slice distance (in mm). Parameter estimates (showing the amount of signal change measured in arbitrary units) of BOLD signal response for the anticipation of loss greater than anticipation of neutral condition were extracted from this bilateral putamen cluster for both mothers and their daughters, and plotted in the scatter graph.

### Neural concordance

We conducted a series of partial correlations to test the association between mothers' and daughters' neural data, controlling for daughter's age. Not surprisingly, motor regions including supplementary motor area and pre/post-central gyri showed no significant associations between mothers' and their daughters' neural response ($rs < 0.206$, $ps > 0.221$). Only bilateral putamen showed a significant association between mothers' and their daughters' neural response to the anticipation of loss [$r(35) = 0.404$, $P = 0.013$; Figure 2] across both groups [RSK/RMD group: $r(12) = 0.537$, $P = 0.048$; CTL group: $r(20) = 0.492$, $P = 0.020$]. This association remained significant after controlling for mother and daughter psychotropic medication use [$r(33) = 0.40$, $P = 0.02$].

### Group differences in bilateral putamen concordance

To test whether the RMD/RSK and CTL groups differed from each other in their association between mothers' and daughters' putamen response to loss, we conducted a moderation analysis to test the interaction of mothers' neural data and group status (RSK/RMD and CTL) in predicting daughters' neural data after controlling for daughters' age. This interaction term was not significant, indicating that the RSK/RMD and CTL groups do not differ in the association between mothers' and daughters' putamen response to loss ($B = -0.018$, $SE = 0.282$, $t(33) = -0.064$, $P = 0.949$). Finally, we explored differences in mean activation between the RSK/RMD and CTL groups in this region. Whereas RMD and CTL mothers did not differ in putamen response to loss [$t(36) = -0.834$, $P = 0.410$], RSK daughters showed significantly lower putamen response to loss than did CTL daughters [$t(36) = 2.385$, $P = 0.022$].

### Developmental influences on bilateral putamen concordance

There was no significant interaction between mothers' putamen response to loss and daughter's age in predicting daughters' putamen response to loss, indicating that daughter's age does not moderate the association between mothers' and daughters' putamen response to loss [$B = -0.208$, $SE = 0.147$, $t(34) = -1.414$, $P = 0.166$]. There was a significant interaction between mothers' putamen response to loss and pubertal status in predicting daughters' putamen response to loss [$B = 0.667$, $SE = 0.283$, $t(32) = 2.355$, $P = 0.025$). Specifically, for those girls who were relatively later in pubertal development at the time of assessment (1 s.d. above the mean, corresponding to Tanner Stage 4.152, and above), higher mothers' putamen response to loss predicted a higher daughters' putamen response to loss. In contrast, for those girls who were less sexually mature at the time of the initial assessment (1 s.d. below the mean, corresponding to Tanner Stage 2.404, and below), there was no association between mothers' and daughters' putamen response to loss. Finally, for girls at the mean value of Tanner Stage (corresponding to Tanner Stage 3.278), there was no association between mothers' and daughters' putamen response to loss.

### Correlations between putamen concordance and depression symptomatology

The degree of similarity between mothers' and daughters' putamen response to loss was not significantly related in either group to the BDI scores of mothers [CTL: $r(20) = 0.19$, $P = 0.44$; RMD: $r(15) = -0.40$, $P = 0.14$] nor the CDI scores of daughters [CTL: $r(23) = 0.24$, $P = 0.26$; RSK: $r(15) = 0.50$, $P = 0.06$].

## Discussion

This is the first study to examine the association, or concordance, between mothers' and daughters' neural patterns of functional activation during a reward processing task. Given the role of aberrant reward processing in the onset and maintenance of depression, we examined functional activation in response to the anticipation of reward and loss in non-depressed mothers with a history of recurrent depression and their never-disordered daughters, as well as in mothers without past or

current depression and their never-disordered daughters. We first identified ROIs involved in the anticipation of reward and loss across all mother-daughter pairs. Within each of these ROIs, we examined the association between mothers' and daughters' neural response, and the interaction between group status and mothers' neural response in predicting daughters' neural response. We found a significant association between mothers' and daughters' putamen response to the anticipation of loss that was similar across the RSK/RMD and CTL groups. We also found that pubertal status of the daughter, but not age, moderated this association such that the developmentally mature daughters exhibited putamen responses to loss that were more similar to their mothers' putamen responses to loss, whereas early pubertal daughters and their mothers did not exhibit such putamen concordance. We found no association between mothers and their daughters in activations in motor regions, including pre/post central gyrus, or bilateral thalamus, suggesting a unique role of the putamen in the maternal transmission of reward learning/responsivity. Finally, we found no association between mother-daughter putamen concordance and concurrent depression severity in mothers or daughters.

The putamen, with the caudate, comprises the dorsal striatum, and has been shown in both human and non-human primate research to be integral to goal-directed behavior and, in particular, to reinforcement learning (Packard and Knowlton, 2002; O'Doherty *et al.*, 2004; Haruno and Kawato, 2006; Balleine *et al.*, 2007). This learning is facilitated by dopamine release in the dorsal striatum when individuals are presented with cues associated with rewarding stimuli. More specifically, the dorsal striatum is posited to play a critical role in learning stimulus-action-outcome associations. The putamen is involved primarily in stimulus-action coding, whereas the caudate plays a stronger role in prediction-error signaling (Haruno and Kawato, 2006; Balleine *et al.*, 2007). As expected, we replicate earlier findings showing that RSK girls show decreased putamen response to loss than do CTL girls. These results inform the current study by highlighting putamen activation in response to loss as a potential intergenerational mechanism that, in depressed mothers, could contribute to the development of depression in their at-risk daughters. In this context, we sought to test whether the differences we identified previously and replicated in the present study were due to concordance between mothers and their daughters in fMRI activation. We found that although RMD mothers did not show significantly reduced putamen response relative to CTL mothers (possibly due in part to treatment exposure), both RSK and CTL daughters showed putamen function similar to that exhibited by their mothers, suggesting a pattern of genetic or learned heritability in this region. If putamen response to loss is related to reinforcement learning patterns, it is not surprising that CTL and RSK daughters show patterns of response similar to those exhibited by their mothers. It is noteworthy, however, that anomalies in reinforcement learning have been found to be associated with depression (Eshel and Roiser, 2010); thus, if a daughter's neural response is similar to a maladaptive response pattern exhibited by her depressed mother, this may be a mechanism underlying the intergenerational transmission of risk for depression. Degree of concordance was not associated with severity of depression across all mothers or daughters (perhaps due in part to treatment exposure in the remitted mothers). Degree of concordance was marginally associated, however, with CDI scores in the RSK daughters. This association was in the opposite direction as predicted (lower concordance was associated with higher CDI scores). Given the small sample size of the RSK group ($n = 15$), this finding must be replicated in a larger sample. It is possible that degree of concordance predicts future, rather than concurrent, severity of depression in daughters; this possibility should be examined in future longitudinal research. It will be equally important in future research to examine how the putamen findings reported in the present study are integrated within the functioning of the reward circuitry as a whole, potentially by investigating concordance of mother-daughter functional connectivity.

Interestingly, the association between mothers' and daughters' putamen response to loss was moderated by pubertal status. This suggests that as daughters become more sexually mature, their neural response to loss becomes more similar to that exhibited by their mothers. It is important to note that this association was not moderated by chronological age, suggesting that it is puberty-related changes in reward-circuitry, specifically, that underlie mother-daughter concordance. Investigators have found pubertal status to be a stronger predictor of the onset of depression than is chronological age (Angold *et al.*, 1998). Indeed, researchers have shown that puberty, and associated adrenal and gonadal hormones, have a significant impact on the development of reward circuitry (Op de Macks *et al.*, 2011; Braams *et al.*, 2015; Peters *et al.*, 2015; Wilbrecht *et al.*, 2016). It is likely that the association between reward system dysfunction and depression emerges or strengthens following this puberty-driven remodeling of reward circuitry (Forbes *et al.*, 2010). In future research, investigators should recruit early- and later-pubertal adolescent girls in order to assess explicitly the strength of mother-daughter concordance across this developmental period and its relation to the onset of depression.

We also found that group status did not moderate the association between mothers' and daughters' neural response. In a similar analysis of a larger group of mother-daughter pairs from this study, LeMoult, *et al.* (2015) found that although mothers and daughters exhibited concordant patterns of diurnal cortisol production, the association between mothers' and daughters' cortisol production was equivalent across groups. More specifically, both RMD mothers and their RSK daughters exhibited heightened cortisol production across the day relative to CTL mothers and their daughters. Their findings suggest that mothers transmit hypercortisolemia to their daughters. Similarly, our results suggest that blunted response to the anticipation of a potential loss is transmitted from depressed mothers to their daughters, perhaps through inheritance or through learning, supporting the model in which depression-related neural function is comparably concordant across all mothers and their daughters, regardless of mothers' psychiatric history (Yamagata *et al.*, 2016). Given the role of anomalous reward processing and reinforcement learning across a number of different forms of psychopathology (Corral-Frías *et al.*, 2015; Whitton *et al.*, 2015), it is possible that this maternal transmission of putamen response confers risk for a broad range of disorders beyond major depression. It will be important for researchers to examine this pattern of maternal concordance across offspring at risk for psychopathologies that are characterized by reward dysfunction, such as bipolar disorder, schizophrenia and substance abuse.

A unique aspect of our sample is that the RMD mothers were not in a depressive episode during their participation in the study, which may explain why they did not show the expected blunted striatal response often documented in depressed relative to non-depressed individuals. It is possible that if we had studied a currently depressed sample of mothers, the degree of neural concordance between mothers and their daughters would have been higher, and degree of concordance may have

been associated with current depression symptoms. It is also noteworthy that we documented mother-daughter concordance in putamen response in anticipation of loss, but not in anticipation of reward. The reward and loss conditions involve a similar degree of learning stimulus-action associations, and both offer the opportunity for a successful trial (in the form of winning points in the reward condition or *not* losing points in the loss condition). Indeed, a recent analysis of reward and loss processing interpreted decreased striatal response to the anticipation of loss in depression as an indicator of 'enhanced loss-related associated learning in depression' (Ubl *et al.*, 2015). Thus, greater associations between mothers' and daughters' putamen response to loss may indicate that loss-related learning is a trait marker or potential vulnerability to developing MDD.

Although we documented a strong pattern of concordance between mothers' and their biological daughters' putamen response to loss, we cannot determine the extent to which this similarity is due to genetic and/or to environmental influences. There is strong evidence for both genetic and environmental contributions to putamen structure (Goldman *et al.*, 2008; Stokes *et al.*, 2013; Hibar *et al.*, 2015); thus, the similarity between mothers' and their daughters' putamen response could plausibly be due to shared genetic material and/or to the daughters implicitly modeling their mother's patterns of reinforcement learning. Growing evidence indicates that throughout childhood, stress and emotion regulation in children occurs through the process of co-regulation, which entails interactions between children and their caregivers in which the caregivers regulate the children's emotions through reciprocal interactions (Hofer, 1994; Calkins and Hill, 2007). Finally, there are also multiple mechanisms of non-genetic inheritance through which behaviors or function can be transmitted non-genetically from parent to offspring (Toth, 2014). These mechanisms of transmission can be further explored by studying children reared by non-biological parents. A recent review of intergenerational neuroimaging study designs by Ho *et al.* (2016) outlines suggestions for future research aiming at delineating familial contributions to disease endophenotypes at the level of neural function and structure. Ho *et al.* propose that through studying the offspring of *in vitro* fertilization (IVF) born via surrogacy or donor sperm/eggs, investigators will be able to better elucidate genetic and environmental contributions to neural endophenotypes.

This is the first study to examine the association between mothers' and daughters' neural patterns of functional activation during a reward processing task. Nevertheless, there are limitations of this investigation that need to be addressed in future work. First, although we found strong evidence of mother-daughter concordance in a neural structure implicated in reinforcement learning, our sample size is relatively small. Because this is the first study on mother-daughter concordance in brain function, future studies in larger samples are needed to replicate our findings and assess whether the concordance patterns we identified hold for other similar constructs implicated in depression (e.g. rumination). Second, given the absence of differences between the RSK/RMD and CTL groups in the association between mothers' and daughters' putamen response to loss, future studies should recruit larger samples of mothers and their daughters independent of the mother's diagnostic history in order to examine whether neural responses underlying different types of associative learning are similar in mothers and daughters. This will allow researchers to examine the generalizability of these findings to a broader population. In this context, it is important to note that seven of the RMD mothers were taking psychotropic medication on the day of the scan, which may have contributed to the lack of difference between CTL and RMD mothers' putamen response to gain and loss. It is noteworthy, however, both that mothers who were taking psychotropic medication did not differ in their putamen response to loss from unmedicated mothers, and that we found a similar pattern of concordance across mothers and daughters after controlling for medication status. Future studies should recruit only medication-free participants in order to eliminate any effect of psychotropic medications on brain function. Finally, investigators pursuing this line of research should include father-son, father-daughter, and mother-son comparison analyses in order to examine the specificity of the mother-daughter concordance in putamen response documented in this study.

In sum, we found a significant association between mothers' and daughters' putamen response to the anticipation of loss that was similar across the RSK/RMD and CTL groups. We found no association between mothers and their daughters in motor regions including pre/post central gyrus and bilateral thalamus, suggesting a unique role of the putamen in the maternal transmission of reward learning/responsivity. These results suggest that reward processing are inherited or learned through putamen response, and have important implications for advancing our understanding of disorders characterized by neural and behavioral disturbances in reward processing, such as major depression. The current findings are significant in highlighting a potential mechanism through which risk for depression is transmitted from mother to daughter, and in identifying a possible neural target for intervention.

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