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Longitudinal Pathways Linking Family Risk, Neural Risk Processing, Delay Discounting, and Adolescent Substance Use

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Abstract

Background: Current theories in neuroscience emphasize the crucial role of individual differences in the brain contributing to the development of risk taking during adolescence. Yet, little is known about developmental pathways through which family risk factors are related to neural processing of risks during decision making, ultimately contributing to health risk behaviors. Using a longitudinal design, we tested whether neural risk processing, as affected by family multi-risk index, predicted delay discounting and substance use.

Method: 157 adolescents (aged 13–14 years at Time 1, 52% male) were assessed annually three times. Family multi-risk index was measured by socioeconomic adversity, household chaos, and family risk-taking behaviors. Delay discounting was assessed by a computerized task, substance use by questionnaire data, and risk-related neural processing by blood-oxygen-level-dependent (BOLD) responses in the amygdala during a lottery choice task.

Results: Family multi-risk index at Time 1 was related to adolescent substance use at Time 3 (after controlling for baseline substance use) indirectly through heightened amygdala sensitivity to risks and greater delay discounting.

Conclusions: Our results elucidate the crucial role of neural risk processing in the processes linking family multi-risk index and the development of substance use. Furthermore, risk-related amygdala activation and delay discounting are important targets in the prevention and treatment of substance use among adolescents growing up in high-risk family environments.

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Keywords

family multi-risk index; risk processing; delay discounting; substance use; functional neuroimaging

Developmental neuroscience theories emphasize the importance of examining brain function to explain individual differences in health risk behaviors such as substance use (Kim-Spoon, Kahn, et al., 2017). Despite emerging evidence linking maladaptive brain development to risk factors in the family environment such as low socioeconomic status or SES (Farah, 2017), little is known about the role of neural processes in developmental pathways connecting family environment to health risk behaviors. In the current longitudinal investigation, we examined whether neural risk processing (i.e., functional brain activation to high risk options) was affected by family multi-risk index (i.e., socioeconomic adversity, chaotic household, and family risk-taking behaviors), and whether it in turn would predict delay discounting and substance use behaviors in adolescence.

We focused on socioeconomic adversity and family risk taking (i.e., delinquent or substance using behaviors by family members) as key family risk factors that may be associated with adolescent risky decision making. Socioeconomic adversity can affect risky decision making through its effects on affective systems. Low SES adolescents are exposed to contextual stress associated with living in more chaotic and unpredictable environments (Evans, Gonnella, Marcynyszyn, Gentile, & Salpekar, 2005). In such stressful environments, adolescents may often experience negative affect (such as anger, frustration, and fear) which may make them more susceptible to risk taking. As suggested by the somatic marker hypothesis (Bechara & Damasio, 2005), stress-related emotions would interfere with somatic markers—i.e., emotional factors that are relevant to the task, such as experiencing and anticipating a reward or punishment—that are supposed to guide the decision in an advantageous direction. Indeed, prior research has shown that young adults with high levels of early childhood stress (measured by stress experiences across several life domains such as school, peer relationships, parent-child relationships) exhibited reduced activation in reward circuitry (putamen and insula) during anticipation of potential losses and also made more disadvantageous and risky decisions, compared to their counterparts with low levels of early childhood stress (Birn, Roeber, & Pollak, 2017).

Exposure to risk-taking behaviors in the family environment may heighten risky decision making. Though no prior research has directly examined the association between family risk-taking behaviors and adolescent risky decision making, the extant theoretical and empirical work suggests that parents transmit self-regulation (with low levels often associated with risk taking) to their children genetically and through socialization (e.g., Bridgett, Burt, Edwards, & Deater-Deckard, 2015). There also is evidence indicating similarity between family risk-taking behaviors and adolescent risk-taking behaviors. For example, there is a clear association between parent and sibling substance using behaviors and adolescent substance use (Hill, Hawkins, Catalano, Abbott, & Guo, 2005). In another longitudinal study, family aggression (i.e., spousal and parent-child aggression) exposure in early adolescence was related to not only to externalizing behaviors but also to larger right

amygdala volume and stronger amygdala-frontolimbic (resting-state) connectivity in late adolescence (Saxbe et al., 2018). Taken together, these findings indicate suboptimal risk-related decision making among those exposed to risk-taking behaviors in the family environment.

Reviewing past research on family risk factors and neural processes related to risky decision making, we note several critical gaps and limitations. First, although the harmful effects of socioeconomic adversity on brain development has been well-documented, evidence is based largely on structural imaging studies in early childhood, indicating effects of low SES on diminished hippocampal and amygdala volumes (see Farah, 2017 for review). Emerging research on SES and brain structure in adolescence has presented mixed findings. One study found no significant effects of SES on brain structural development during adolescence (Whittle et al., 2017), whereas another study found a significant association between lower SES and smaller amygdala volume among adolescents but not children (Merz, Tottenham, & Noble, 2017). Studies of brain functions (i.e., task-based brain activity or connectivity) related to socioeconomic adversity in adolescence are rare, but much needed. Experiencing socioeconomic adversity may produce particularly potent effects in the adolescent brain, due to rapid development and greater plasticity of developing brain systems during the teen years (Tottenham & Galván, 2016). To address this first major gap, we examined family multi-risk index and functional brain measures during adolescence.

Second, studies on SES and adolescent brain functions show a link with neural correlates of reward sensitivity (Romens et al., 2015) and cognitive control (Spielberg et al., 2015) among adolescents—but there has been no study examining the effects of socioeconomic adversity on “risk-related neural processing”. Similarly, most prior work on the effects of stress exposure (broadly measured by cumulative stressful life events) on brain functions has focused on reward-related neural circuitry such as ventral striatum, measured during the outcome phase—i.e., during the anticipation or the reception of a reward following decision making (Birn et al., 2017; Hanson, Hariri, & Williamson, 2015; Romens et al., 2015). However, in value-based decision making, risky choices are driven by not only neural computations associated with the value of rewards, but also the probability of receiving such rewards (Mohr, Biele, & Heekeren, 2010). For instance, an adolescent may make risky decisions either because the outcome of a decision is strongly valued, or because the outcome has a high chance of occurring. Prior research has demonstrated that neural processing of risk (i.e., the likelihood of potential reward values) predicts real-world risk-taking behaviors in adolescents both cross-sectionally and longitudinally (Kim-Spoon, Deater-Deckard, et al., 2017; Maciejewski et al., 2018). Furthermore, evidence suggests that individual differences in neural responses to risk may be influenced by family risk factors such as household chaos (Lauharatanahirun et al., 2018). In the current study, we focused on family multi-risk index and its links with risk-related neural processing.

Third, prior research on the effect of socioeconomic adversity on functional brain activation has examined *a priori* regions of interests (ROIs). Examining only previously identified ROIs can lead to a biased and inappropriately constrained characterization of anatomy (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006). To address this limitation, we used a group level whole brain general linear model (GLM) analysis to identify risk-related

activation in response to high risk options of chosen gambles (measured during the decision phase). This analysis was used to determine our functional brain ROIs.

We reasoned that risk-related neural processing would be associated with individual differences in impulsive decision (shown in delay discounting), which in turn would lead to elevated substance use. Specifically, based on prior studies, we expected that heightened risk-related amygdala activation, in part from the diminished top-down control due to excessive stress (Arnsten, 2009), would be related to greater delay discounting. Delay discounting describes the process by which future reinforcers are devalued as a function of the amount of time until those rewards can be obtained, and is thought to underlie impulsive decision making involved in substance use and addiction (Bickel et al., 2007). A growing literature suggests the critical role amygdala plays in delay discounting (Pessoa, 2010). There is evidence showing that increased amygdala activity and decreased dorsolateral prefrontal cortex activity (during delay discounting decision making) due to cognitive challenges (i.e., high-load vs. low-load working memory blocks) predicted greater increases in delay discounting rates (Aranovich, McClure, Fryer, & Mathalon, 2016). In turn, research indicates that high delay discounting is associated with high levels of substance use among adolescents (Kim-Spoon, McCullough, Bickel, Farley, & Longo, 2015). Therefore, although no studies have investigated neurobehavioral processes that explain the link between family multi-risk index and adolescent substance use, evidence from prior research implies that risk-related neural processing may be associated with heightened delay discounting behavior and ultimately increased substance use.

In the current longitudinal study, we investigated pathways through which family risk factors are associated with risk processing in the brain, which further contributes to delay discounting and substance use behaviors during early to middle adolescence. We first examined the association between family multi-risk index (characterized by socioeconomic adversity, household chaos, and family risk-taking behaviors) and functional brain activation during decision making for high-risk options. Based on prior work showing enhanced reactivity in affective regions (e.g., amygdala, ventral striatum) to affective stimuli, we hypothesized that higher family multi-risk index scores would be associated with heightened reactivity in affective regions to high risk options. We further hypothesized that hyperactivity in affective regions would predict high delay discounting, which in turn would be associated with increased substance use.

Method

Participants

Participants were 157 adolescents (52% male) aged 13 to 14 years ($M = 14.13$, $SD = 0.54$) at Time 1, participating annually in the longitudinal study over three years ($M = 15.05$, $SD = 0.54$ at Time 2 and $M = 16.08$, $SD = 0.55$ at Time 3). The sample was representative of the region for household income and race/ethnicity. About 82% were White, 12% were African American, and 6% were in other ethnic groups, and median household income was in the \$35,000–\$50,000 range. Based on an income-to-needs (ITN) ratio (the level of household income divided by the poverty threshold for family size), half of the sample was deemed to be either “poor” (25% of the sample, with $ITN < 1$) or “near poor” (25%, $ITN < 2$). Of the

remaining “non-poor” families (50%, ITN = 2), nearly half of these (20% of the total sample) had very high discretionary income (ITN > 4). Exclusion criteria were claustrophobia, history of head injury resulting in loss of consciousness for >10 minutes, orthodontia impairing image acquisition, and contraindications to magnetic resonance imaging. Between Time 1 and Time 3, 18 adolescents withdrew from the study for reasons such as: lost contact ($n = 8$), declined participation ($n = 8$), and other ($n = 2$). Multivariate logistic regression revealed that those who withdrew and those who continued did not differ on age, sex, race, or income (all p s > .23). Some participants were excluded for the following reasons (leaving 135 adolescents for the main analyses): excessive motion (> 3mm in any direction; $n = 10$), incomplete scanning ($n = 4$), and lack of variability in choice (i.e., choosing safe or risky option > 85% of the time; $n = 8$).

Procedure

Participants were recruited by advertisement methods including flyers, recruitment letters, and e-mail. Adolescent participants and their primary caregivers visited the laboratory to complete behavioral measures and MRI scans at three annual time points and were compensated for their participation. All adolescent participants provided written assent and their parents provided written permission for a protocol approved by university’s institutional review board.

Measures

Family Multi-Risk Index.—At Time 1, socioeconomic adversity was assessed by parents’ reports on their and their spouse’s (when applicable) number of years of education (mean of parent and spouse education), family income (1 = *none* to 15 = *\$200,000 or more per year*), and whether they received any public income assistance (1 = *yes* or 2 = *no*). In addition, adolescents reported on the level of household chaos using the 6-item (1 = *definitely untrue* to 5 = *definitely true*) Confusion, Hubbub, and Order Scale (CHAOS; Matheny, Wachs, Ludwig, & Phillips, 1995) at Time 1. Mean scores were calculated with higher scores indicating higher levels of confusion and disorganization in the home. The reliability of the scale was relatively low in the present sample ($\alpha = .59$), which is consistent with prior research which has demonstrated reliable predictive and construct validity of this scale (e.g., Asbury, Dunn, Pike, & Plomin, 2003). Finally, family risk-taking behaviors at Time 1 was assessed with the mean of 10-items of the *Family History of Antisocial Behaviors* subscale from the PhenX Toolkit (Hamilton et al., 2011), which was designed to measure family risk factors for risk taking (Arthur et al., 2007). Adolescents reported on various risk-taking behaviors (i.e., substance use and delinquent and criminal behaviors) that adults and family members in their lives (e.g., 1 = *none* to 5 = *five or more adults*). The scale was reliable ($\alpha = .76$).

The standardized scores (reverse-coded as necessary) of lower parental education, lower family income, receipt of public aid, higher household chaos, and higher family risk-taking behaviors were averaged so that higher scores indicated family environment that was more conducive to adolescent risky decision making.

Delay Discounting.—Reward-dependent decision making was assessed using a computerized delay discounting task (Johnson & Bickel, 2002) at Time 2. Adolescents were presented with a series of hypothetical decisions involving intertemporal choices between an immediate monetary reward and a larger monetary reward with a delay. The amount for the delay was held constant at \$100 across four delays: one day, one week, one month, and one year. Individual discounting functions were calculated using hyperbolic k values as an index for discounting rate, then log-transformed to correct for non-normal distribution. Higher scores were indicative of greater delay discounting.

Adolescent Substance Use.—Adolescents reported frequency of cigarette, alcohol, and marijuana use at Time 1 and Time 3 using a substance use index adapted from the Youth Risk Behavior Survey (Kann et al., 2014). This index consists of three items such as, “Which is the most true for you about using alcohol?”, using a 6-point response scale ranging from 1 (*never used*) to 6 (*usually use every day*). A polysubstance use composite score was computed at each time point using an average of all three items, with higher scores indicating greater use, with the rates of adolescents who endorsed using substances being: 16% for cigarette, 26% for alcohol, and 8 % for marijuana at Time 1, and 26% for cigarette, 40% for alcohol, and 24% for marijuana at Time 3. Scale reliability was acceptable ($\alpha = .75$ at Time 1 and $\alpha = .61$ at Time 3).

Lottery Choice Task.—Adolescents completed a modified lottery choice task at Time 1 in which they made choices between pairs of gambles (Holt & Laury, 2002) while their BOLD response was monitored using fMRI (see Figures 1A and 1B). The Holt and Laury menu of gambles was designed to measure risk preferences using an economic risk-elicitation paradigm, and such economic lottery choice tasks have been widely used in cognitive neuroscience to investigate decision-making processes (Huettel, Stowe, Gordon, Warner, & Platt, 2006). Each gamble included a high and low monetary outcome, and each was associated with a specific probability. Probabilities associated with potential payoffs were presented using pie charts in order to maximize comprehension of numerical information for adolescent participants. For each option, there were 10 slices with each corresponding to a probability of 10%. Monetary outcomes and probabilities varied across trials. The associated risk for each gamble was measured using coefficient of variation (CV), a scale-free metric calculated by dividing the standard deviation by expected value. For each pair of gambles, one option was always riskier (higher CV) than the other (lower CV). Since probabilities were the same for both gambles in a given trial, with the difference between low and high monetary amounts distinguishing the level of risk between options (i.e., the option with the smaller difference in values indicated lower risk, compared to the option with the larger difference in values). In order to incentivize performance, participants were compensated based on their actual winnings from 5 randomly selected trials (Smith, 1976). Participants completed a total of 72 trials, and were told that each trial was independent from all other trials and was equally likely to be selected for compensation. The task took approximately 30 minutes to complete.

Imaging acquisition and analysis.—Functional neuroimaging data were acquired on a 3T Siemens Tim Trio MRI scanner with a standard 12-channel head matrix coil. Structural

images were acquired using a high-resolution magnetization prepared rapid acquisition gradient echo sequence with the following parameters: repetition time (TR) = 1200 ms, echo time (TE) = 2.66 ms, field of view (FoV) = 245×245 mm, and 192 slices with the spatial resolution of 1×1×1 mm. Echo-planar images were collected using the following parameters: slice thickness = 4mm, 34 axial slices, FoV = 220×220mm, TR = 2 s, TE = 30 ms, flip angle = 90 degrees, voxel size = 3.4×3.4×4 mm, 64×64 grid, and slices were hyperangulated at 30 degrees from anterior-posterior commissure. Imaging data were preprocessed and analyzed using SPM8 (Wellcome Trust Neuroimaging Center, University College London). For each scan, data were corrected for head motion using a six-parameter rigid body transformation and realigned. The mean functional image was co-registered to the anatomical image, then the anatomical image was segmented and registered to the MNI template and functional volumes were normalized using parameters from the segmented anatomical image, and were smoothed using a 6mm full-width-half-maximum Gaussian filter.

Within a GLM, at the subject level, decision period and outcome events were modeled with a duration of 4 and 2 seconds, respectively (Figures 1A and 1B). A parametric regressor of decision phase BOLD activity corresponding to the CV of chosen gambles was included in the model in order to assess neural responses of risk processing. A parametric regressor of the outcome phase was also included corresponding to whether subjects received the high or low value outcome. Additional regressors of no interest included the button press and six motion regressors. At the group level of the GLM, whole brain analysis was conducted to determine how CV for chosen gambles related to BOLD response. A cluster-level family-wise error (FWE) corrected level of $p < .05$ and a cluster-defining primary threshold of $p < .001$ were used to correct for multiple comparisons.

Results

Whole brain analysis revealed that during the decision phase, BOLD responses in bilateral insula, dorsal anterior cingulate cortex, and ventral striatum were associated with magnitude of risk. Group-level multiple regression analysis was conducted to assess the link between family multi-risk index and risk-related neural responses during the decision phase. Family multi-risk index for each participant was regressed against parametric risk-related responses across the whole brain. Results from this analysis showed that adolescents with higher family multi-risk index scores exhibited increased activation in the right amygdala in response to chosen gambles that were higher (relative to lower) risk during the decision phase of the task (see Figure 1C and Table 1). The conjunction of both prior evidence implicating the right amygdala to be involved in representing family adversity in the adolescent brain (Roth, Humphreys, King, & Gotlib, 2018; Saxbe et al., 2018), and whole brain analysis identifying the right amygdala as a neural correlate of risk processing especially in adolescents from high-risk family environments, $t(133) = 4.09$, $p(FWE) < .05$, led to our focus on the right amygdala in subsequent analyses. Eigenvariate values were extracted for the peak voxel coordinates of the right amygdala cortex using a 6mm sphere (right: $x = 36$, $y = 2$, $z = -23$).

Prior to testing the hypothesized model, two univariate outliers on right amygdala activation that deviated more than 3.29 *SD* from the mean were Winsorized. Table 2 presents descriptive statistics and zero-order correlations among the study variables. Multivariate GLM analyses indicated that demographic variables (age, sex, and race) did not have significant effects on the predicted variables (all $ps > .128$), thus they were not included in the model as covariates. To investigate the impact of incomplete data (i.e., missing at random), we performed logistic regression analysis testing if missingness (i.e., either missing Time 2 or Time 3 data, or both) was related to any of the study variables. Missingness was not related to any demographic characteristics such as sex and race (White vs. non-White) or study variables including Time 1 family multi-risk index, Time 1 substance use, and Time 1 amygdala activation ($p = .13 \sim .76$).

We conducted longitudinal mediation analyses using structural equation modeling (SEM) in *Mplus* version 8 (Muthén & Muthén, 1998–2017), with Full Information Maximum Likelihood (FIML) estimation with robust standard errors (MLR) to account for missing data and non-normal distributions. For testing indirect effects, we calculated bias-corrected bootstrap confidence intervals (CIs) with maximum likelihood estimation (bootstrapping is not available for MLR) using 10,000 bootstrapping samples (Preacher & Hayes, 2008).

In the hypothesized model, we were interested in testing the indirect effects linking Time 1 family multi-risk index to Time 3 substance use (after controlling for baseline substance use) mediated through Time 1 amygdala activation during the risk-processing task and Time 2 delay discounting. We first analyzed a full model that estimated all possible regression paths, which was a saturated model (i.e., RMSEA = .00; CFI = 1.00; $\chi^2 = 0$, $df = 0$, $p = 0$). Then we trimmed the model by removing non-significant paths that were not part of the hypothesized links (the path from Time 1 amygdala activation to Time 3 substance use, the path from Time 1 family multi-risk index to Time 2 delay discounting, the path from Time 1 substance use to Time 1 amygdala activation, and the path from Time 1 substance use to Time 2 delay discounting). The nested model comparison between the full model and the trimmed model using the Satorra-Bentler scaled chi-square statistic (Satorra & Bentler, 2001) indicated that our hypothesized model (i.e., the trimmed model; RMSEA = .00, CFI = 1.00, $\chi^2 = 4.25$, $df = 4$, $p = .373$) was the preferred, more parsimonious model over the full model ($\chi^2 = 4.25$, $df = 4$, $p = .373$).

In our hypothesized model, we estimated the indirect effects from Time 1 family multi-risk index to Time 3 substance use as mediated through Time 1 amygdala activation and Time 2 delay discounting, as well as the direct effect from Time 1 family multi-risk index to Time 3 substance use (while controlling for baseline substance use by estimating the autoregressive effects of Time 1 substance use on Time 3 substance use). In addition, the covariance between Time 1 substance use and Time 1 family multi-risk index was estimated. Results revealed (see Figure 2) that higher Time 1 family multi-risk index scores were related to higher Time 1 amygdala activation ($b = .02$, $SE = .005$, $p < .001$), which in turn was related to higher Time 2 delay discounting ($b = 6.80$, $SE = 2.95$, $p = .021$). Higher Time 2 delay discounting in turn was related to higher Time 3 substance use ($b = .14$, $SE = .04$, $p = .027$), even after controlling for the effect of Time 1 substance use on Time 3 substance use ($b = 1.00$, $SE = .11$, $p < .001$). There was a significant indirect effect from Time 1 family multi-

risk index to Time 3 substance use via amygdala and delay discounting (bias-corrected bootstrap 95% CI [.001; .045]). The direct effect from Time 1 family multi-risk index to Time 3 substance use was not significant ($b = .04$, $SE = .10$, $p = .672$), whereas Time 1 family multi-risk index and Time 1 substance use were significantly correlated with each other ($b = .12$, $SE = .05$, $p = .01$).

We performed supplemental analyses to explore whether the family multi-risk index, amygdala activation, and delay discounting may predict differentially across different substances by testing the mediation model separately for cigarette, alcohol, and marijuana use. In all three models, the path from Time 1 family multi-risk index to Time 1 amygdala activation and the path from Time 1 amygdala activation to Time 2 delay discounting were significant, whereas the direct effect of Time 1 family multi-risk index on Time 3 substance use was not. Differences across the three substances were found in the path between Time 2 delay discounting and Time 3 substance use (after controlling for Time 1 substance use). We found that for cigarette and alcohol use, after taking into account the significant autoregressive effects of Time 1 cigarette/alcohol use, Time 2 delay discounting was not a significant predictor of Time 3 cigarette/alcohol use. The model fits were good (RMSEA = .05, CFI = .99, $\chi^2 = 5.26$, $df = 4$, $p = .262$ for cigarette use; RMSEA = .00, CFI = 1.00, $\chi^2 = 3.08$, $df = 4$, $p = .544$ for alcohol use). For marijuana use, Time 2 delay discounting predicted Time 3 marijuana use ($b = .17$, $SE = .07$, $p = .014$). The indirect effect of Time 1 family multi-risk index on Time 3 marijuana use via Time 1 amygdala activation and Time 2 delay discounting was significant (bias-corrected bootstrap 95% CI [.002; .074]). The model fits were good (RMSEA = .07, CFI = .95, $\chi^2 = 6.56$, $df = 4$, $p = .161$).

Additionally, we examined the independent effects of each risk factor in the family multi-risk index (i.e., socioeconomic adversity, household chaos, and family risk-taking behaviors) on risk-related activation (see Appendix S1-S3). The results revealed that these separate risk factors were related to regions typically involved in visual processing and attention (e.g., postcentral gyrus, inferior parietal cortex, fusiform gyrus, and cerebellum) rather than affective-related regions.

Discussion

Associations between adverse family environments and deleterious health outcomes are often observed (Bickel, Moody, Quisenberry, Ramey, & Sheffer, 2014), yet the neural processes underlying these associations are not well understood. Addressing this gap in adolescence is particularly important given the maturational changes occurring during this period that may render some especially susceptible to stress-related alterations in mechanisms that underlie risky decision making (Tottenham & Galván, 2016). The current longitudinal study presents the first evidence for risk-related neural processing and delay discounting as pathways through which family risk factors are related to the development of substance use behaviors.

Our neuroimaging data revealed that adolescents with higher family multi-risk index scores (i.e., socioeconomic adversity, household chaos, and family risk-taking behaviors) exhibited heightened amygdala activation in response to chosen options that involved higher levels of

risk for receiving potential rewards. The amygdala is known to determine the value of stimuli in the environment and engage in alerting and attention functions (Pessoa, 2010). For adolescents growing up in unpredictable and harsh environments (as in families laden with socioeconomic adversity, household chaos, and exposure to risky behaviors), their amygdala may pick up such environmental cues and respond to environmental demands by vigilance and attention. Our finding of the association between family risks and heightened right amygdala activation during risk processing provides an important extension of prior findings suggesting amygdala development is vulnerable to stress-dependent disruptions. Research indicates that adolescents who experienced family aggression or maltreatment show greater right amygdala volume (Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014; Saxbe et al., 2018). In addition, individuals with exposure to adversity in the family environment exhibited heightened amygdala activation related to threat or arousal. For example, young adults who experienced poverty during adolescence exhibited greater amygdala activation during effortful regulation of negative emotion compared to their counterparts (Kim et al., 2013). Also, the risk factors of life stress and family history of depression predicted increases in amygdala reactivity to fearful faces over two years among adolescents (Swartz, Williamson, & Hariri, 2015).

Interestingly, in a study of female adolescents' neural responses to reward using a monetary reward task, childhood financial disadvantage was significantly associated with heightened responses in the medial prefrontal cortex, but not the amygdala or striatum, during reward anticipation (Romens et al., 2015). Another study demonstrated that young adults with high childhood stress exposure showed blunted neural activation in the reward network (e.g., ventral and dorsal striatum) when processing cues signaling loss, compared to those with low childhood stress exposure (Birn et al., 2017). Considering our finding in the context of results of prior research focusing on reward circuitry may suggest specificity in the role of the amygdala during risk processing—it plays a key role in evaluating the rewarding or aversive value of environmental stimuli and its function is heightened in high-stress contexts. That is, while the effects of low SES may be more evident in the activation of the medial prefrontal cortex during reward anticipation phase (as shown in Romens et al., 2015), the effects of broader family risks (such as socioeconomic adversity, household chaos, and family risk-taking behaviors) may be more evident in the amygdala during the risk-related decision making phase (as shown in the present study).

Furthermore, hypoactive striatum while processing cues signaling loss (as shown in Birn et al., 2017) and hyperactive amygdala while evaluating high-risk options (as shown in the present study) may suggest suboptimal brain functioning associated with poor decision making among those who have been exposed to impoverished, harsh environments. The data reported here highlight that growing up in stressful home environments, laden with insecurity associated with scarce resources and threat associated with aggressive family behaviors, may predispose adolescents for increased vigilance of high-risk options during decision making under uncertainty. Perhaps, amygdala functioning is particularly vulnerable to stressful home environments because the amygdala is attuned to uncertainty due to its role in interpreting and making sense of its surroundings (Pessoa, 2010). Given that the development of amygdala volume is at its peak during adolescence (Wierenga et al., 2014),

adolescence may be a critical period for the effect of family risk factors on amygdala development.

Our results elucidated the processes by which family multi-risk index is associated with the development of adolescent substance use via neural risk processing and behavioral delay discounting. The significant association between amygdala activation during risk processing and later delay discounting makes sense, because the amygdala is one of the important nodes in the valuation network that interfaces with the control network to determine delay discounting decision making (van den Bos et al., 2014). Our finding clarifies that family environments characterized by socioeconomic adversity, household chaos, and family risk-taking behaviors may espouse greater delay discounting by undermining (or biasing) amygdalar functions involved in determining the value of stimuli in the environment. Although we did not have a direct measure of the effects of family multi-risk index on cognitive control, it is also plausible that family risk factors might tax attentional resources and cognitive control (e.g., Mullainathan & Shafir, 2013), and such cognitive strain undermines prefrontal cortex regulation of the amygdala (Aranovich et al., 2016; Sheridan, Sarsour, Jutte, D'Esposito, & Boyce, 2012) thus resulting in heightened amygdala activation during valuation-based decision making. Choosing behavior with potentially negative consequences because of more immediate rewards may be “adaptive” for adolescents growing up in resource-scarce, unpredictable, and chaotic family environments. However, such an adaption to family context may be maladaptive in a different context. An example of this is discounting the value of delayed health outcomes and engaging in immediately reinforcing activities such as using drugs, which increases the odds of subsequent substance use disorder.

The results of our supplemental analyses revealed that separate risk factors did not activate affect-related brain regions. This finding may speak to the emergent effects of multiple risks such that these individual family risk factors function in a cumulative fashion to influence amygdala activation, suggesting the powerful impact of the combination of risk factors in the family multi-risk index compared to examining each potential risk in isolation. Our finding converges with extant studies using multiple risk models to examine risks in sociodemographic and family domains and child adjustment, showing that the combination of risk factors across multiple domains maximizes prediction of variance compared to specific risk factors or particular combination of them (e.g., Deater-Deckard, Dodge, Bates, & Pettit, 1998; Trentacosta et al., 2008). Of most relevance, prior studies of stressful life events and brain activity suggest significant effects of stressful life events (i.e., sum or average of the severity ratings across multiple stressful life events) on reward-related ventral striatum activity (Hanson et al., 2015) and threat-related amygdala activity (Swartz et al., 2015), although these previous studies did not test the effect of each life event separately. Nevertheless, the limited finding that the individual risk factors did not show consistent significant effects on amygdala activity calls for future replications.

We also observed that changes in marijuana use showed a stronger association with delay discounting than cigarette and alcohol use. One interpretation of this finding is that marijuana use is thought to have more serious future consequences due to the illicit nature of marijuana in the region, and thus adolescents' impulse control abilities played a more

prominent role in using marijuana compared to cigarette and alcohol. We note that no study has examined the potentially differential roles of delay discounting across different substances using a prospective longitudinal sample of adolescents. Instead, prior research comparing substance-dependent adults with healthy control adults indicates that delay discounting is more closely related to nicotine and alcohol dependence than marijuana dependence (e.g., Johnson et al., 2010). Our finding provides preliminary, yet important evidence that delay discounting may play an important role for the initiation and progression of marijuana use during early to middle adolescence. In future studies, it would be informative to clarify whether the role of delay discounting may vary depending on the severity of substance use or the perception of negative future consequences.

There are several limitations of the current study. First, our correlational analyses do not allow us to infer causality in the identified relationships, or to rule out passive genetic transmission of risk processing. Second, we primarily focused on examining amygdala functioning during risk processing. Future research may find it informative to examine multiple cognitive and affective networks as well as frontolimbic connectivity.

Finally, although we primarily focused on examining risk factors in family environment in the current study, we acknowledge other social relationship factors (e.g., peer substance use, parenting practices) that may contribute to the development of risky decision making and behaviors in adolescence.

In conclusion, our findings illustrate how adolescent brain development is influenced by family risk factors and related to risk taking. The family multi-risk index was related to heightened amygdala sensitivity to risks, which in turn was predictive of subsequent delay discounting and substance use. Such alterations to the developing amygdala can have cascading effects as a result of the amygdala's projections to the ventral striatum and the late-developing prefrontal cortex (Ernst, Pine, & Hardin, 2006), promoting the development of substance use disorder. Understanding the developmental emergence of neural and behavioral phenotypes associated with health risk behaviors can provide a powerful tool for identifying individuals susceptible to health risk behaviors. Our results imply that risk-related amygdala activation and delay discounting may be important targets in the prevention and treatment of substance use among at-risk adolescents growing up in family environments characterized by socioeconomic adversity, household chaos, and family risk-taking behaviors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Individual differences in brain development during adolescence are critical to the development of health risk behaviors.
- Developmental pathways through which family risk factors are related to neural processing and substance use behaviors are not clearly understood.
- Our structural equation modeling analyses suggest that higher family multi-risk index scores were related to higher levels of adolescent substance use (after controlling for baseline substance use) indirectly through heightened amygdala sensitivity to risks and greater delay discounting.
- Risk-related amygdala activation and delay discounting are important targets in the prevention and treatment of substance use among adolescents growing up in high-risk family environments.

Figure 1.

A) In the lottery choice task, adolescents were asked to choose between pairs of uncertain gambles. For each gamble, there was a high and low monetary outcome, each associated with a specific probability. The associations between outcomes and probabilities are represented with corresponding colors (orange or blue), B) Each trial consisted of a decision phase, a fixation phase, an outcome phase, and an inter-trial-interval (ITI), C) During the decision phase of the economic lottery choice task, adolescents with higher (relative to lower) levels of family multi-risk index scores exhibited increased BOLD responses in the right amygdala to chosen gambles that were of higher relative to lower levels of risk (i.e., coefficient of variation; CV), $t(133) = 4.09$, $p(\text{cluster family-wise error correction}) < .05$.

Figure 2.

Summarized model fitting results of the path model of longitudinal associations among family multi-risk index, neural risk processing, delay discounting, and substance use among adolescents. Standardized estimates are presented. $^*p < .05$; $^{**}p < .001$.

Table 1.

Neural correlates of family environment in response to risk during the decision phase

Cluster #	Region	Size	Peak MNI Coordinates			
			<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>
1	L Hippocampus	55	-33	-7	-20	4.09
	L Fusiform Gyrus		-36	-22	-23	3.64
2	R Amygdala	131	36	2	23	4.09*
	R Fusiform Gyrus		30	-4	35	4.01
	R Hippocampus		24	-13	-14	3.92
3	R Inferior Temporal Gyrus	20	51	-34	-23	3.95
4	L Supramarginal Gyrus	16	-51	-34	31	3.66

Note: MNI, Montreal Neurological Institute; L, Left; R, right. Size refers to the number of voxels in the cluster.

* Denotes activations that survive whole brain family-wise error multiple comparisons correction at a cluster threshold of $p < .05$

Table 2.

Descriptive Statistics and Bivariate Correlations of Family Multi-Risk Index, Neural Risk Processing, Delay Discounting, and Substance Use

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Range	M (SD)
1. Family multi-risk index T1																-0.82–2.51	-0.001(0.55)
2. Household chaos	.25**															1.17–4.83	2.44(0.66)
3. Family income	.63**	.11														2.00–15.00	10.96(2.64)
4. Parents' years of education	.68**	.16	.54**													9.00–17.00	14.44(1.85)
5. Receipt of public aid	.70**	.15	.60**	.47**												1.00–2.00	1.76(0.43)
6. Family risk-taking behaviors	.72**	.25**	.30**	.35**	.30**											0.50–4.40	1.64(0.78)
7. Right amygdala activation T1	.35**	-.03	.20*	.24**	.20*	.27**										-0.11–0.10	-0.01(0.03)
8. Delay discounting T2	.19*	.16	.10	.13	.16	.15	.20*									-4.32–0.24	-2.10(1.05)
9. Substance use T1	.44**	.15	.06	.17	.18*	.37**	.11	.02								1.00–3.33	1.25(0.49)
10. Cigarette use T1	.34**	.13	.07	.20*	.20*	.30**	.07	.10	.82**							1.00–5.00	1.17(0.56)
11. Alcohol use T1	.32**	.14	-.05	.09	.08	.28**	.06	.03	.85**	.54**						1.00–4.00	1.38(0.67)
12. Marijuana use T1	.46**	.20*	.15	.23*	.19*	.31**	.09	-.05	.79**	.51**	.48**					1.00–4.00	1.14(0.55)
13. Substance use T3	.36**	.22*	.03	.14	.12	.38**	.18	.16	.68**	.56**	.61**	.49**				1.00–4.00	1.60(0.73)
14. Cigarette use T3	.29**	.13	.19*	.20*	.22*	.23*	.16	.07	.63**	.67**	.51**	.38**	.66**			1.00–5.00	1.37(0.74)
15. Alcohol use T3	.22*	.21*	-.13	.03	-.04	.31**	.13	.13	.43**	.25**	.50**	.28**	.74**	.21*		1.00–4.00	1.88(1.03)
16. Marijuana use T3	.31**	.15	.04	.12	.13	.31**	.13	.16	.53**	.43**	.41**	.46**	.85**	.44**	.41**	1.00–6.00	1.56(1.12)

Note. For bivariate correlations, family income, years of education, and public aid were reverse coded so that higher scores indicate greater risks.

* $p < .05$ ** $p < .01$.