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Neural Activation During Risky Decision-Making in Youth at High Risk for Substance Use Disorders

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Abstract

Risky decision-making, particularly in the context of reward-seeking behavior, is strongly associated with the presence of substance use disorders (SUDs). However, there has been little research on the neural substrates underlying reward-related decision-making in drug-naïve youth who are at elevated risk for SUDs. Participants comprised 23 high-risk (HR) youth with a well-established SUD risk phenotype and 27 low-risk healthy comparison (HC) youth, aged 10–14. Participants completed the balloon analog risk task (BART), a task designed to examine risky decision-making, during functional magnetic resonance imaging. The HR group had faster reaction times, but otherwise showed no behavioral differences from the HC group. HR youth experienced greater activation when processing outcome, as the chances of balloon explosion increased, relative to HC youth, in ventromedial prefrontal cortex (vmPFC). As explosion probability increased, group-by-condition interactions in the ventral striatum/anterior cingulate and the anterior insula showed increasing activation in HR youth, specifically on trials when explosions occurred. Thus, atypical activation increased with increasing risk of negative outcome (i.e., balloon explosion) in a cortico-striatal network in the HR group. These findings identify candidate neurobiological markers of addiction risk in youth at high familial and phenotypic risk for SUDs.

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Conflicts of interest

The authors have no conflicts to declare.

Keywords

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1. Introduction

Decision-making refers to the process of "forming preferences, selecting and executing actions, and evaluating outcomes" (Ernst and Paulus, 2005). Theorists have identified a series of processes that occur during the choice phase of decision-making: initiation, monitoring, and completion of choice-related actions (Reyna and Rivers, 2008). The outcome phase follows, in which individuals learn and process the actual outcomes of their choices (Reyna and Rivers, 2008). Altered decision-making patterns have been observed in individuals with substance use disorders (SUDs), including preference for short-term gains (Grant et al., 2000; Bechara and Damasio, 2002) and riskier options (Lane and Cherek, 2000) and difficulty valuing the probability and magnitude of potential outcomes (Rogers and Robbins, 2001; Paulus et al., 2002; Paulus et al., 2003). Whether these decision-making deficits and their underlying neural substrates are the result of repeated use of drugs of abuse, predate SUDs, or both, remains unclear. Deficits in making choices have been hypothesized to originate from preexisting neurobiological abnormalities (Ernst and Paulus, 2005), while deficits in processing outcomes have been hypothesized to be more likely a consequence of substance use (Redish, 2004). To address this hypothesized distinction, the neural basis of decision-making must be better characterized in drug naïve individuals, with the eventual goal of longitudinally assessing neural activity in candidate regions as SUDs develop, as has been done with other imaging modalities (Norman et al., 2011).

Because fewer than 15% of adolescents develop lifetime SUDs (Huang et al., 2006), targeting youth at high familial and phenotypic risk for SUDs might illuminate underlying neural mechanisms influencing the development of SUDs. Given that the mean onset of SUDs is age 14 (Swendsen et al., 2012), assessing decision-making in high-risk preadolescent youth is warranted. Multiple addiction risk models have converged on the finding that youth with externalizing disorders [e.g., attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD)], particularly those with a family history of addiction, are at elevated risk for the development of SUDs (Tarter et al., 2003; Zucker, 2008; Iacono et al., 2008; King et al., 2009). For example, among 10–12 year old boys followed to age 19, the risk model implemented here predicted SUDs with 85% accuracy and accounted for 50% of the variance in drug use (Tarter et al., 2003). Thus, we attempt to maximize risk for SUD development according to these models by recruiting a high-risk sample with *both* SUD family history and childhood externalizing psychopathology. While this complex risk phenotype does not allow for the dissociation of neural effects of externalizing psychopathology from those related to a family history of addiction, its high predictive power for SUD development is clinically significant. Findings revealed with this high-risk sample (versus healthy comparisons) warrant future investigations designed to disentangle the impact of externalizing disorders and familial factors.

Most of the risky decision-making literature in externalizing disorders has focused on either adults (Miranda et al., 2009; Matthies et al., 2012; Duarte et al., 2012; Galvan et al., 2013) or youth behavioral outcomes (Drechsler et al., 2008; Fairchild et al., 2009; Drechsler et al., 2010; Schutter et al., 2011). These studies highlight an increased probability of disadvantageous decisions, correlations of risky-decision-making with impaired working memory and a propensity for lower probability/high reward choices in both youth and adults with externalizing psychopathology. Only one study appears to have directly examined the neural basis for risky-decision-making in youth with externalizing disorders (Crowley et al., 2010) and it focused on brain response during the outcome phase. Contrasting cautious low-yield with risky high-yield responses (n=20 adolescents with conduct/SUDs, in remission; n=20 adolescent controls), authors reported decreased activity during reward (anterior cingulate, temporal cortex and cerebellum) and increased activation during loss (orbitofrontal cortex, brain stem and cerebellum) in the conduct/SUD group. Thus, youth with externalizing disorders reliably demonstrate behavioral differences in risky-decision-making, but few studies have addressed the neural underpinnings of these differences.

Several studies have examined neural activation associated with decision-making in youth identified as being at elevated risk for SUDs (Ivanov et al., 2012; Nees et al., 2012; Xiao et al., 2013). In these studies, youth deemed high risk for SUD, either by early/problem use or by family history have been shown to have activation abnormalities in cortical (OFC, insula), limbic and striatal circuits, although findings are inconsistent across studies, potentially due to heterogeneity in psychopathology and substance use. Most work has been conducted in older non-drug naïve youths, which likely confounds neural risk factors with early effects of substance use. Additionally, in this population, no studies have dissociated choice from responses to choice outcomes.

Using the balloon analog risk task (BART), we examined the neural basis of choice and outcome phases of decision-making separately and characterized activation changes as both risk and reward increase across trials. The BART uses financial incentives to model real-world drug and alcohol choices by presenting participants with a series of risky-decisions and has been associated with psychopathy and impulsivity (Hunt et al., 2005), adolescent risk-taking (Lejuez et al., 2003b; Lejuez et al., 2007) and SUDs (Lejuez et al., 2003a; Hopko et al., 2006). In the sample most relevant to the present, youth with externalizing disorders (mean age 16) were found to have behavioral differences, specifically more inflations and more popped balloons, compared to healthy controls (Crowley et al., 2006). The initial version of the BART used in imaging (Rao et al., 2008) was modified from the original (Lejuez et al., 2002) to be able to dissociate choice effects (i.e., choose to inflate or stop) from outcome effects (i.e., successful inflation, burst, and cash out). In healthy adults, fMRI BART studies have revealed that the choice phase of risky-decision making is linked to activation in a meso-limbic frontal network including midbrain, ventral and dorsal striatum, anterior insula, dorsal lateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC) (Rao et al., 2008; Fukunaga et al., 2012) and ventromedial prefrontal cortex (vmPFC) (Fukunaga et al., 2012; Schonberg et al., 2012). Findings associated with the outcome phase have been associated with a similar network involving insula, striatal, cerebellar and medial prefrontal regions (Galvan et al., 2013); Surprising outcomes have been associated with the medial PFC (Jessup et al., 2010). Increased responses to balloon explosions in lateral

prefrontal cortex, insula, ACC and middle temporal gyrus was reported in adults with alcohol use disorders, relative to controls (Claus and Hutchison, 2012). Medial prefrontal activation was also correlated with adult alcohol use during balloon outcomes (Bogg et al., 2012).

The BART has been studied in adolescents (Lejuez et al., 2003b; Lejuez et al., 2007), although only minimally during fMRI and not in the context of addiction risk (Chiu et al., 2012; Telzer et al., 2013b, a). We administered the BART to drug-naïve youth selected for high SUD risk (high risk; HR) and healthy comparisons (HC) during fMRI. The version of the BART used here (Bogg et al., 2012; Fukunaga et al., 2012) included a parametric modulation analysis that allowed for the study of a central question: How neural activation changes as risk for explosion changes. Since deficits in choice selection may predate drug involvement (Ernst and Paulus, 2005; Paulus et al., 2005), we hypothesize that HR youth will demonstrate insensitivity to increasing explosion probability in choice-relevant regions (e.g., anterior cingulate cortex (ACC), inferior frontal gyrus). We also hypothesize that neural response to choice outcomes will be more marked in HR youth in the vmPFC, ACC (Smith et al., 2010; Bogg et al., 2012) and dorsal striatum, given its role in action-reward associations in humans (Balleine et al., 2007) and in prior BART studies (Rao et al., 2008).

2. Methods

2.1. Participants

As detailed previously (Hulvershorn et al., 2013), we recruited right-handed, English-speaking 10–14 year-olds with at least one parent capable of reading and speaking English. To maximize familial risk for SUD development, HR participants were required to be biological offspring of men with past or present SUDs and to have an additional first- or second-degree family member with SUD history. Each HR participant also met DSM-IV-TR criteria for ADHD plus a disruptive behavior disorder [CD, ODD or disruptive behavior disorder, not otherwise specified (DBD NOS)]. More than five lifetime uses of drugs of abuse (including nicotine) or alcohol were exclusionary. HR participants were recruited largely from the community (radio, print and online ads), although a minority of youth were recruited directly from a psychiatric clinic (signs in clinic, notification by intake coordinator).

HC participants had no current or lifetime history of any DSM-IV psychiatric diagnosis or SUDs (exceptions: specific phobias, enuresis, encopresis, learning disorders) and no first-degree relative with a history or current diagnosis of a SUD. HC participants were recruited in response to community postings.

All individuals with *in utero* exposure to drugs or alcohol, per caregiver report, were excluded. Additional exclusion criteria for both groups included psychotic symptoms, pervasive developmental disorders, current depression or mania, or SUDs; psychopharmacologic treatment within the past 2 weeks other than psychostimulants (withheld the days of assessment and scanning, as is routine for pediatric ADHD neuroimaging studies, given little concern for withdrawal symptoms); history of

neurological problems; estimated Full-Scale IQ <75; active or debilitating medical conditions; or MRI contraindications.

2.2. Assessment procedures

Parents completed a phone screen with a research coordinator and were invited in for an assessment if they appeared to meet inclusion criteria. Written consent/assent was obtained in person from at least one parent and the child utilizing Indiana University IRB-approved materials. Rapid urine toxicology screening (Uritox Medical) tested for five illicit drugs (methamphetamine, ecstasy, cocaine, opiates, cannabis). The substance use domain of the Drug Use Screening Inventory (Kirisci et al., 1995) was administered to each child privately.

During the first visit, a trained doctoral-level clinician completed the K-SADS-PL (Kaufman et al., 1997) semi-structured interview separately with parent(s) and child to determine present or lifetime psychiatric diagnoses. Children also completed IQ screening (Wechsler, 1999). Parents completed checklists for Tanner pubertal development staging. Children also completed the child version of the UPPS-P Impulsive Behavior Scale (Zapolski et al., 2010). The UPPS-P-C is a 40-item self-report instrument assessing five distinct tendencies toward impulsive behavior in children and adolescents, including lack of premeditation (i.e., failure to think before acting), lack of perseverance (i.e., failure to complete tasks), sensation seeking (i.e., tendency to seek out new and exciting experiences), negative urgency (i.e., acting rashly in extreme negative emotional states), and positive urgency (i.e., acting rashly in extreme positive emotional states). These five traits are detectible in adolescence (Zapolski et al., 2010) and stable over time (Cyders et al., 2007; Smith et al., 2007); higher scores reflect more impulsive behaviors.

The presence of paternal SUDs was assessed with the substance abuse section of the Structured Clinical Interview for DSM-IV (SCID)-I/Non Patient Edition (First et al., 2002). When the child's father was unavailable for interview, an informant SCID interview was obtained with the available parent. Only subjects with clear evidence supporting or refuting paternal SUD diagnoses were included.

2.3. Imaging procedures

Before the scanning session, participants completed urine drug screening and pregnancy testing (no positives were detected), were instructed to limit movement during scanning and practiced completion of the BART. Participants were scanned on a 3.0 Tesla Siemens Magnetom Tim Trio MRI scanner using a 32-channel head coil. After a short scout scan, a high-resolution 3D magnetization prepared rapid gradient echo (MPRAGE; 160 sagittal slices; 1.0 × 1.0 × 1.2 mm voxel dimension) scan was acquired and used for co-registration and normalization of functional image volumes to Talairach space. A gradient recalled echo (GRE) field-mapping scan followed (echo time [TE]= 25 ms; 35 axial slices (64 × 64 grid); voxel dimension 3.4 × 3.4 × 3.8 mm; 0 mm spacing manually shimmed to ensure optimization of the ventral brain signal). Then, one session of the BART was acquired over 8 min, using a T2*-weighted gradient echo-planar imaging (EPI) sequence (TR/TE 2000/25 ms, flip angle 70°; same slice locations and voxel dimension as GRE field mapping).

2.4. fMRI task

During the BART, participants must decide whether to risk cash rewards that increase with each inflation, or bank the amount and start a new balloon. Fig. 1 presents a schematic of the task. At the beginning of the task, a fixation cross in the center of the screen appeared for 30 s. At the start of each trial, a balloon and a green (e.g., go) decision cue were displayed on the screen. Participants then chose to inflate the balloon (Choose Inflate) or take the accumulated wager (Choose Win; i.e., "cash out") via button pressing. After the response, a jittered delay occurred where no feedback was allowed (modification per Fukunaga et al., 2012). Jitter delays (0, 2000, 4000, or 6000 ms) were chosen by a weighted random selection (30, 12, 5 and 2, respectively). After the delay, the outcome was presented. For Choose Inflate trials, an exploding balloon was shown for 500ms followed by "You Lose!" text for 1000 ms, or a successfully inflated balloon for 500 ms. If the balloon inflated, the decision cue turned red for 1.5, 2.0, or 2.5 s (equiprobable) when no responses were allowed. After each inflation, the chance of balloon explosion increased, identically for each balloon. For Choose Win, "You Win!" was presented for 1000 ms. After a win or a loss, the screen was blank for 2, 3 or 4 s (equiprobable) and then a new balloon appeared. Once the cue turned green, the next trial began. The cumulative earnings were presented at the bottom of the screen during each trial.

We modeled increases in the probability of explosion over successive responses by using a parametric modulator (Fukunaga et al., 2012). Parametric modulation analysis is a specific type of fMRI analysis in which changes in brain activation are examined, as an experimental condition changes. Here, the parametrically modulated fMRI regressor models an assumed linear relationship between probability of explosion and brain activity during each trial. This type of analysis allows for the study of how the increasing risk of explosion is related to changes in brain activity during each trial. We paired an increasing risk of explosion with an increasing wager amount for each successive inflation (whose exact probabilities are unknown to the participant; see Supplementary Table 1). This allowed us to detect systematic changes in the amplitude of the BOLD signal as explosion probability changes.

A maximum of 12 inflation responses were possible for each balloon. Explosions were possible after any of the responses. Participants completed as many trials as they were able during the 8-min scan. Participants could theoretically earn up to $50 if the balloons never exploded and participants always inflated to the maximum. A jitter function was applied between decision and outcome phases of each trial to differentiate decision-making and feedback-related processes (Fukunaga et al., 2012). Participants were instructed to "inflate the balloon as much as you can without popping it" in order to earn money for each unexploded balloon. Participants were told that they won more money for larger unexploded balloons. Their actual earnings were paid in cash following the scan. We simplified the task for use in children by not presenting the wager amount at the onset of each trial (Fig. 1), although they were previously trained that larger balloons were worth more money.

2.5. Behavioral analysis

For each group, the total winnings, total balloons completed and reaction times (in ms) for choices were compared using *t*-tests. In addition, the number of trials with very long

reaction times (defined as >5000 ms) was compared between groups. Balloons were also compared between groups for the following measures: balloons won, balloons exploded, inflations per balloon, minimum/maximum number of inflations and reaction times. Analysis of variance (ANOVA) was performed to examine group (HR vs. HC) by condition (choose win vs. choose inflate) interactions as well as main effects of group. To assess whether behavioral traits correlated with BART performance, UPPS-P-C subscale scores were correlated with the following variables (listed in Table 4) using Pearson's Correlations (averaged per participant): number of inflations per balloon, total number of inflations, total number of exploded, stopped and completed balloons and total average winnings.

2.6. Image analysis

2.6.1. Subject-level analyses—Image preprocessing, using AFNI software (Cox, 1996), consisted of slice-time correction, de-spiking of time series outliers (3dDespike algorithm), motion correction via realignment to the first time point using Fourier interpolation, registering the functional image to the structural image, correction for signal inhomogeneity with field mapping and spatial smoothing with a Gaussian kernel of 6-mm full-width at half-maximum. A general linear regression model (GLM) with random effects was created to estimate event-related responses. Along with six motion parameters and linear and quadratic detrending terms to correct for potential scanner drift, nine regressors that encompassed all potential decisions and outcomes, including parametric modulators when appropriate, and one additional nuisance regressor (reaction time outliers) were generated. Time points with >3.5-mm head displacement were censored (plus the time point before and two after). Participants with >10 time points censored were excluded.

Choice events, aligned to the one repetition time (TR) that included the button press response, were modeled as Choose Inflate (choosing to continue inflating the balloon) or Choose Win (choosing to discontinue inflating and bank money) regressors. *Outcome events* were modeled as the TR that included balloon explosion (Outcome Explode), successful balloon inflation (Outcome Inflate), or the outcome of choosing to discontinue inflations (Outcome Win). Because there were relatively few Outcome Explode events, outliers (1.5*interquartile range) among those participants with fewer than five balloon explosions were excluded from Outcome contrasts (n=3 participants).

For each subject, Choose Inflate and Choose Win conditions were contrasted. For outcome trials, only Outcome Inflate vs. Outcome Explode were contrasted, as these constitute the outcomes (positive or negative) that could follow an identical earlier decision (Choose Inflate). We did not contrast Outcome Win (vs. either Outcome Inflate or Explode) because there was no uncertainty at this point in the trial (i.e., the subject had already banked the reward).

Balloon explosion probabilities (Supplementary Table 1) were included as parametric modulators for each event-type regressor (e.g., Choose Inflate * P(explode), Outcome Inflate * P(explode)), except for Outcome Win, because the probability of explosion no longer applied at this point. The parametric modulator for a given inflation represented the explosion probability at each pump, not the total explosion probability that occurs until the balloon either explodes or is cashed out. Inclusion of parametric modulators accounts, in

part, for the psychological impact of the changing balloon explosion probability across trials.

Trials with reaction time outliers (>5000 ms) were modeled separately, but identically to all other balloons, and treated as nuisance regressors. Activation maps were warped to a standard Talairach atlas for group analyses. For subjects where P(explode) was the same for each explosion (2 HR, 1 HC), modulatory effects could not be separated from effects of the explosion itself, so these participants were excluded from outcome contrasts.

2.6.2. Group level analyses—Contrast maps for choice (Choose Inflate vs. Choose Win) and outcome (Outcome Inflate vs. Outcome Explode) were obtained separately from subject-level coefficients. To test for between-group differences on the contrasts, we carried out condition (e.g., Choose Inflate vs. Choose Win) by group within-subjects ANOVAs (using 3dMVM in AFNI) on activation intensities derived from the GLM ("Analysis of BOLD signal, without Parametric Modulation"). In addition, choice and outcome ANOVAs with parametric modulators (P(explode)) were also conducted ("Parametric Modulator Analysis"). Activation intensities from each subject were extracted from significant clusters.

Separately, to examine the potential influence of IQ or socioeconomic status (SES) on the findings, activation intensities from significant clusters were tested with analysis of covariance (ANCOVA) using SES (defined using family income on a 1–5 scale, where **1** = <$20,000; **2** = $20,000 – $40,000; **3** = $40,000 – $60,000; **4** = $60,000 – $80,000; **5** = > $80,000; Table 1) and full-scale IQ as covariates. Only clusters which remained significant ($p < 0.05$) after accounting for covariates are reported as primary findings. Incidentally, all clusters remained significant after accounting for covariates.

Multiple comparisons associated with this whole-brain voxel-wise analysis were addressed using cluster-wise thresholds. Individual voxels were considered significant at $p < 0.01$, and a Monte Carlo simulation (AlphaSim) was again used to determine that cluster size (k) > 216 voxels corrected for group-level significance ($p < 0.05$).

3. Results

3.1. Participants

Fifty-six right-handed male and female participants aged 10–14 years old completed the protocol. Six participants were excluded from all analyses for the following reasons: (1) two HR participants had >10 motion-censored time points; (2) two HR participants had high global signal variance across the time series, likely non-neural artifact; and (3) two HC participants had >10 trials with reaction times exceeding 5000 ms. Groups did not differ on motion in the scanner (Table 1).

Groups were matched on age, gender, and Tanner stage, but they differed on IQ and SES (Table 1). Psychotropic medication treatment histories are presented in Table 1. See Table 2 for clinical characteristics of the child participants and Table 3 for paternal SUDs.

3.2. BART performance

Groups did not differ on task outcomes, except for reaction times (Table 4), where HR youth were faster on win trials ($F(1, 46)=7.27$, $p=0.01$). Twelve participants (11 HC; 1 HR) required modeling with the nuisance regressor for outlier reaction time, though no participant had more than three outliers. Several BART performance outcomes (Table 4) were correlated with self-report measures of impulsivity (UPPS-P-C; Table 1). Negative urgency (the tendency to act rashly during negative emotions) and lack of premeditation (not thinking before acting) were positively correlated with number of inflations per balloon ($R=0.35$, $p=0.01$ for negative urgency and $R=0.33$, $p=0.01$ for lack of premeditation). This suggests that these traits are associated with a strategy of inflating the balloons more (i.e., maximizing reward) and not avoiding balloon explosions (i.e., avoiding punishment). In fact, negative urgency was also positively related to total earnings ($R=0.39$, $p=0.04$), suggesting that this strategy on the BART was effective.

3.3. Imaging results

For main effects of task condition, with and without parametric modulator analysis, see Supplementary Fig. 1 and Supplementary Table 2. Group effects are reported below.

3.3.1. Choice conditions—No main effects of group or group × condition interactions were found for the choose contrasts (Choose Win vs. Choose Inflate).

3.3.2. Outcome conditions

Parametric modulator analysis: There were main effects of group in a cluster in the bilateral ventromedial PFC (vmPFC), such that HR participants had greater activation in both conditions, as balloon explosion probability increased (for all voxels: $F(1,40)>7.22$, $p<0.01$; $k>216$ voxels; Table 5, Fig. 2).

Two clusters showing a group × condition interaction spanned the ACC/ventral striatum and inferior frontal gyrus(IFG)/anterior insula ($F(1,40)>7.22$, $p<0.01$; $k>216$ voxels; Table 5; Fig. 3). In these clusters, as explosion probability increased, post hoc analyses revealed that the HR participants had increasing activation and HCs decreasing activation on the Outcome Explode trials (ACC/striatum: $t(40)=13.5$, $p=0.001$; IFG/insula: $t(40)=11.1$, $p=0.002$), but no group differences on the Outcome Inflate trials.

Analysis of BOLD signal, without parametric modulators: There was a group × condition interaction in the left occipital cortex (for all voxels: $F(1,43)>7.22$, $p<0.01$; $k>216$ voxels; Table 6). This interaction was driven by greater activation for HR group than the HC group on the Outcome Explode, but not on the Outcome Inflate condition.

3.3.3. Functional connectivity—To further explore the findings in the striatal cluster where activity differed between groups on the outcome contrast (Fig. 3), a functional connectivity analysis was used to examine the time-series correlation between activity in this cluster and all other voxels. This analysis demonstrated that during the outcome contrast, the striatal cluster was highly functionally correlated with prefrontal and posterior (i.e., occipital) regions for both groups (see Supplemental Fig. 2). However, group

differences were only found in a cluster in the thalamus ([7,-21, 4], *k*=269; peak *t* =3.3 voxels, $p<0.01$), where the HC group had a stronger negative correlation that the HR group.

4. Discussion

Using the BART in a complex childhood phenotype known to be at elevated risk for SUD development, we characterized brain activation underlying risky decision-making that parallels real-world drug- and alcohol-related choices. In these HR youth, decision-making deficits that lead to drug use are likely already at play. Here we examined routine activation intensity across contrasts, as well as the main focus of the study, i.e., the change in activation seen as the probability for balloon explosion changes. The parametric analyses examining changes in activation revealed intriguing group differences in sensitivity to reward/explosion. We found no group differences in brain activation during the decision-making phase (Choose Win vs. Choose Inflate). Rather, brain activation differed between groups solely during the outcome phase (Outcome Inflate vs. Outcome Explode). Consistent with other MRI studies comparing groups, we report no differences in behavioral outcomes, apart from reaction time. This is likely due to different explosion probability distributions used in MRI studies (vs. behavioral studies) used because of time constraints (Galvan et al., 2013), although the BART has not been studied in children as young as those in our sample. Of note, earlier BART studies have found that despite the lack group behavioral differences, brain activation on this task was predictive of future addiction-pertinent behavior (Bogg et al., 2012; Kohno et al., 2015). This work suggests the need for inclusion of additional behavioral measures of decision making in future studies.

We do report that BART performance was correlated with traits underlying impulse control. Specifically, traits associated with rash action and with failure to think through one's actions were associated with maximizing rewards rather than avoiding punishment. Although this might be effective in the short term (increased earnings on the BART task, for instance), this strategy is likely to be maladaptive in the long run (Cyders et al., 2007).

Our results suggest that neural mechanisms underlying the choice to proceed with riskier outcomes are not clearly separable in high- vs. typical-risk pediatric samples. It seems unlikely, however, that choice-related deficits are absent in HR youth. Thus, we speculate that because Choose Inflate neural responses were so large relative to Choose Win responses (Supplementary Fig. 1), a ceiling effect may have obscured any group difference. There may also be the possibility of false negative findings, given our relatively stringent cluster size threshold. In addition, this version of the task presents notice of reward as "You Win!" rather than auditory and visual stimuli of coins falling, as has been used in prior versions (Lejuez et al., 2002). It may be that the attenuated reward stimuli resulted in diminished activation for HR youth, resulting in a failure to observe group differences on the choice contrast. Finally, we cannot rule out the possibility that, developmentally, the neural-basis for choice may not yet appear aberrant in HR youth. Additional study with other tasks that probe the choice phase of decision-making are needed to validate this finding. Thus, neural response to outcomes appears to be a more sensitive endophenotypic target than choice activity during decision-making in preadolescents.

For our primary finding (Outcome Inflate vs. Outcome Explode contrasts), we observed group differences in fMRI analyses (with or without parametric modeling), despite little apparent difference in task performance. Group differences emerged in the vmPFC, as predicted. This difference appeared to be driven by increased activation in the HR group, as risk of balloon explosion increases. The vmPFC has been firmly associated with decision-making deficits, particularly in the context of uncertain outcomes (Fellows and Farah, 2007). Stimulant and alcohol abusers who failed to learn from their mistakes during decision-making were found to have abnormal activation in the vmPFC (Bechara et al., 2001). In this case, increasingly atypical vmPFC activation as balloon explosion becomes more likely suggests that HR youth may utilize an abnormal neural strategy to process outcomes, potentially hampering their ability to learn from mistakes.

We also report group × condition interactions on the outcome contrasts in ventral striatum/ACC and anterior insula/inferior frontal gyrus, with explosion trials driving the findings. In the striatal/ACC cluster, disappointing outcomes were associated with greater activation in HR youth, even as the outcomes became less surprising. The ventral striatum has been found to be most active when uncertainty about an outcome was maximal (Heekeren et al., 2007). It may also play a role in forming expectancies that inform future decisions (van der Meer and Redish, 2009). Hence, the inverse pattern of activation observed between groups on the explosion outcomes in the ventral striatum raises the possibility of deficits in reward learning, particularly in the context of uncertain outcomes. Of note, in rats, the ventral striatal encoding of reward outcomes was correlated with later risk-taking behavior (Sugam et al., 2014), suggesting a neural mechanism underlying future risk-taking in HR youth (Pasupathy and Miller, 2005; Lau and Glimcher, 2007; Yamada et al., 2011). In the case of the BART, striatal activity was greater for unexpected explosions in the HC group, possibly because these trials required an “update” to learned patterns. In the HR sample, inadequate neural encoding of the relationship between balloon size (i.e., risk) and explosion (i.e., adverse outcome) could explain the activation patterns seen across increasing probability of explosion. With early drug experimentation, failure to learn from adverse consequences of drug use could promote ongoing use, a consequence particularly relevant to the HR group.

As reviewed above, anterior insula/inferior frontal gyrus activation has been reported during risky decision-making. Decreased activation has been reported in drug-using populations during risky decision-making and was attributed to executive functioning deficits (Stewart et al., 2014), similar to those present in our HR group. These regions are particularly relevant to balloon explosions due to their connections with limbic regions which process emotional responses to unpleasant outcomes (Jabbi et al., 2008; Jabbi and Keysers, 2008). Thus, these findings point to the need for further study of the role of emotional responses to adverse outcomes, particularly as they pertain to the development of SUDs.

4.1. Limitations

This study is based on the assumption that externalizing psychopathology in offspring of males with SUDs portends risk for the development of SUDs. It remains to be seen if HR youth in this sample will develop SUDs at higher rates than controls, although

phenotypically similar youth have been shown to have substantially elevated rates of SUD development when prospectively followed into their late teens/early twenties. Further, given the small sample size, gender effects are unexamined here and warrant future exploration, although groups were matched on gender. Second, to screen out those with more than five lifetime substance use occasions, we relied on self-report plus drug screening at the assessment and scanning. Third, most HR participants have been treated with psychotropic medications, raising the possibility that brain activation may be impacted by past treatment. While psychostimulants have been used to treat ADHD symptoms in a subset of these youth, the doses and route of administration (i.e., oral) differ substantially from those typical of stimulant abuse. Less than one third of participants with ADHD were currently taking medication, and medication was held for at least 24 hours before scanning. Thus while these results may be impacted by medication effects, the majority of participants were medication free for this study. It would have been prohibitively difficult to recruit a psychotropic naïve sample meeting our other inclusion criteria. Fourth, the HR group had lower SES and lower IQ; however, secondary covariate analyses accounted for these variables. Only two findings appeared to be substantially influenced by these covariates. It is also worth noting that lower IQ appears to be part of comorbid severe externalizing disorders (Moffitt, 1993) and recruiting equal-IQ groups might also reduce other important group differences. Fifth, because disruptive behavior disorders and a family history of SUDs co-occur in our HR group and are not present at all in the HC group, we are unable to attribute the etiology of our findings specifically to either factor. However, these findings are promising and warrant further study using designs that can tease apart the effects of externalizing disorders and family history of SUDs. Sixth, the version of the task used here and in other BART imaging studies do not provide auditory and visual stimuli of coins dropping when the participant ‘cashes out.’ This may attenuate the rewarding effects during our outcome contrasts, although we do report within group and between group brain activation intensity differences on those contrasts. Finally, due to concerns for time in the scanner for pediatric participants, children completed the BART over one 8-min session (vs. two 8-min sessions). This limited the number of occurrences of all events and resulted in decreased statistical power for more rare events, such as explosions. The shortened version of the task may have also limited our ability to detect behavioral group differences. Therefore, behavioral and neuroimaging findings warrant replication.

4.2. Conclusions

These data support the hypothesis that aberrant brain activation in cortical and striatal regions relevant to risky decision-making may predate drug use and serve as a testable marker of SUD risk in those with elevated liability for SUD development. Examining parametric modulation of balloon explosion probability is an innovative and high-yield approach to characterizing group differences, as it allows for the study of neural responsivity to risk changes. Such analyses have been done only sparingly in adults and have not been reported in youth. In our pediatric sample, outcome contrasts revealed differences between groups, while choice contrasts did not, suggesting future examination of the choice phase with additional tasks are needed. Thus, using novel task adaptations (i.e., separating choice from outcome, examining risk parametrically), this study identified regions engaged during rewarding versus disappointing outcomes. Aberrant activation while processing outcomes of

decisions may impact adolescent responses and subsequent learning for all manner of adolescent choices, including experimentation and ongoing use of drugs of abuse. Future work following high-risk samples prospectively may determine if activation differences are actual biomarkers predictive of SUD development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Neural response to outcomes of risky-decisions appears to be a more sensitive endophenotypic target than activity while making choices in high risk preadolescents compared to healthy comparisons.
- Atypically increased activation in the vmPFC in high-risk youth, a region associated with risky decision making, was found prior to the use of drugs of abuse.
- Striatal activation abnormalities suggest a failure to learn from adverse consequences, a finding particularly relevant to youth known to be at elevated risk for the development of substance use disorders.

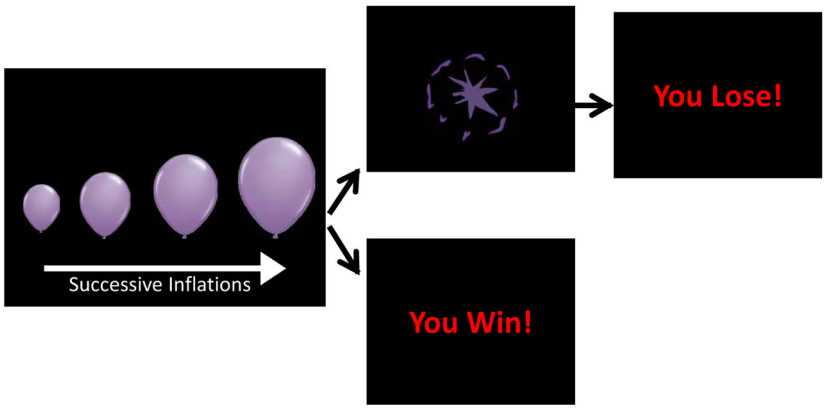

Fig. 1.

A schematic of the Balloon Analog Risk Task (BART) showing successive balloon inflations (i.e., a series of Choose Inflates) that either end in Outcome Inflate (“You Win!”) or an Outcome Explode (“You Lose!”).

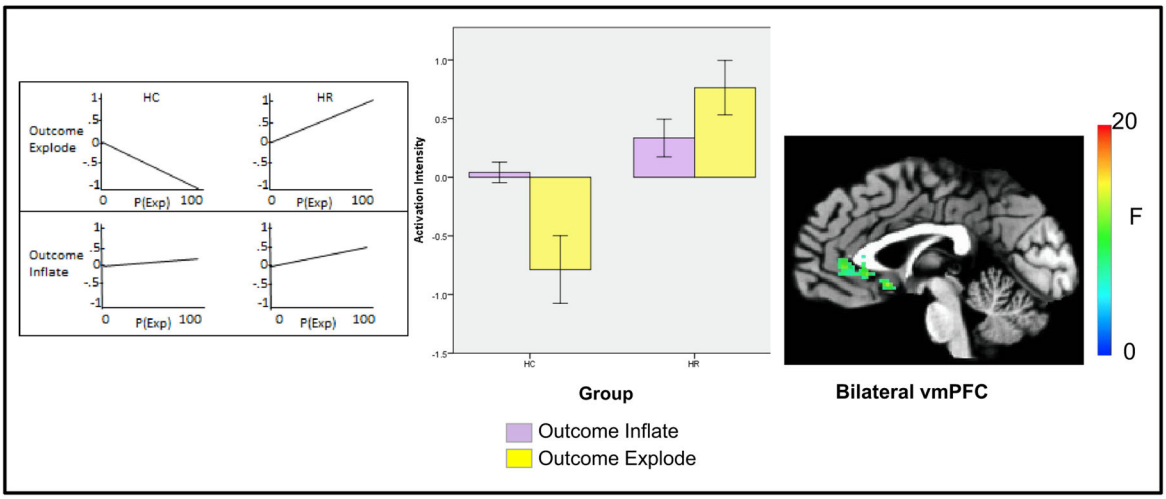

Fig. 2.

Group differences (healthy comparisons (HC) vs. high risk (HR)) on the parametrically modulated outcome contrast. Group differences, driven by increasing activation intensities as explosion probability increases in the HR group, were found in a bilateral cluster in the ventromedial prefrontal cortex (vmPFC; Table 5). Bar graphs plot activation intensities (*y*-axis) from the cluster according to condition (Outcome Inflate or Outcome Explode) and group (HC or HR). Line graphs illustrate the relationship between probabilities of balloon explosion (*x*-axis) vs. activation intensities of the blood oxygen level dependent (BOLD) signal in the cluster (*y*-axis).

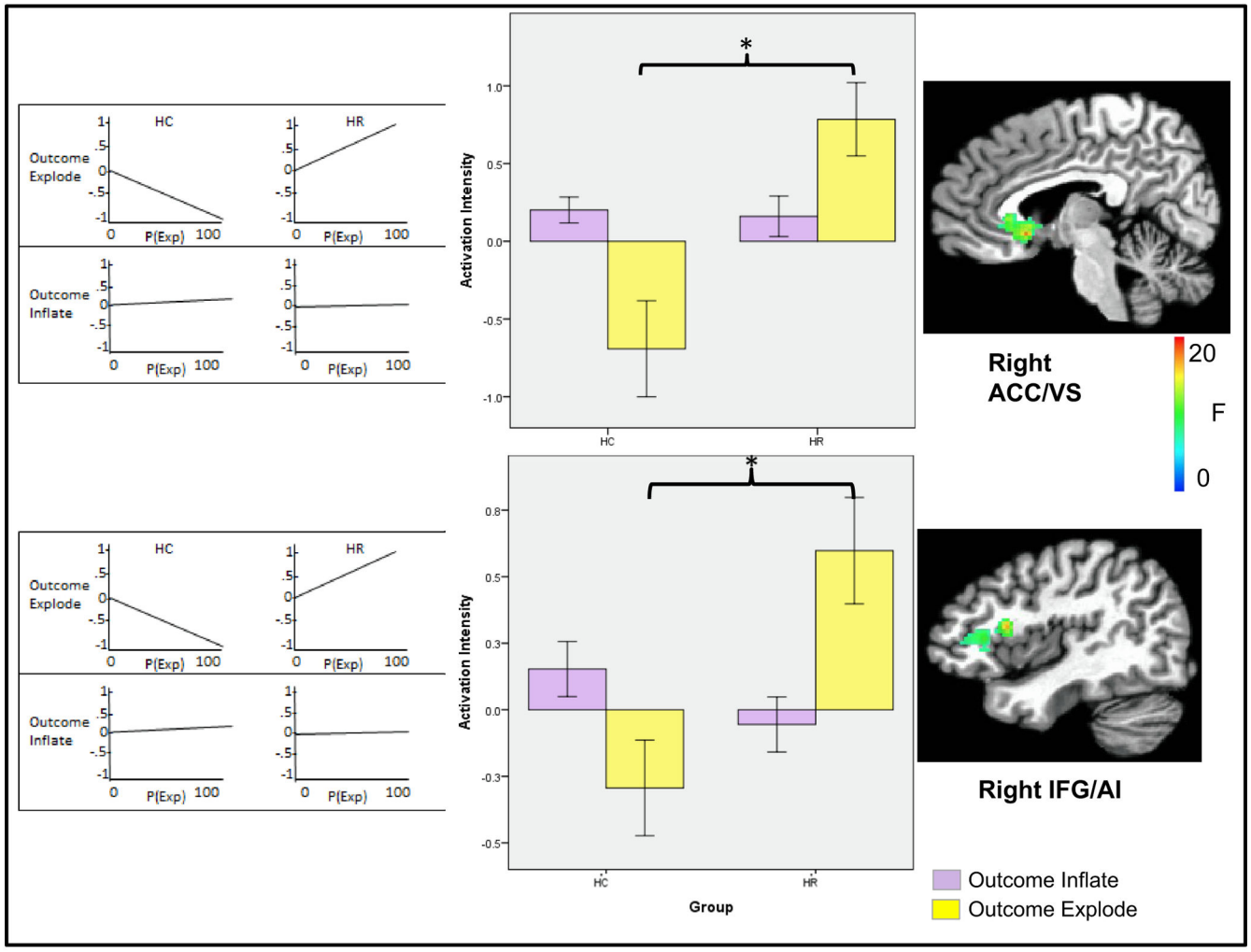

Fig. 3.

Group × Condition interactions, on the parametrically modulated outcome contrast. Outcome Interactions were found in: 1. Right ventral striatum and anterior cingulate cortex (ACC) and 2. Right anterior insula (AI)/inferior frontal gyrus (IFG; Table 5). In both clusters, high risk youth had increasing activation on the explosion trials. Asterisks indicate group differences ($p<0.01$). Bar graphs plot activation intensities (y-axis) from each cluster according to condition (Outcome Inflate or Outcome Explode) and group (healthy comparison (HC) vs. high risk (HR)). Line graphs illustrate the relationship between probability of balloon explosion (*x*-axis) vs. activation intensities of the blood oxygen level dependent (BOLD) signal for each cluster (*y*-axis).

Table 1

Demographic, head motion, data censoring, drug use and UPPS-P-C scores by group.

	HR (n = 23)	HC (n = 27)	*p*
Number of Females (%)	13 (48%)	9 (39%)	0.532
Age	12.3 (1.3)	11.9 (1.2)	0.206
Race			0.293
Caucasian	6 (26%)	12 (44%)	
African American	14 (61%)	9 (33%)	
Other	3 (13%)	6 (22%)	
IQ	96.5 (12.1)	112.2 (10.1)	< 0.001
SES: Family Income Level	1.5 (0.9)	3.8 (1.3)	< 0.001
Tanner Stage	2.9 (1.3)	2.7 (1.2)	0.500
Max MRI Head Displacement (mm)	1.37 (0.88)	0.96 (0.64)	0.066
Timepoints Excluded for Motion	1.9 (4.2)	0.5 (1.4)	0.140
Participants with Motion Censoring	5	3	0.444
Participants with Any Drug Use	2	1	0.459
Total Number of Drug Use Instances	2	3	NA
Participants with Psychotropic Medication:			
Past Treatment	19(68%)	0	
Present Treatment	8(28%)	0	
UPPS-P-C Subscales			
Lack of Premeditation	17.4 (4.4)	14.4 (4.3)	0.017
Positive Urgency	19.0 (6.3)	13.2 (4.1)	0.001
Negative Urgency	20.2 (4.8)	15.1 (5.5)	0.001
Sensation Seeking	21.4 (5.5)	22.2 (6.1)	0.650
Lack of Perseverance	17.3 (3.3)	15.2 (3.0)	0.023

Table 2

DSM-IV diagnoses by group.

FHR Group (n=23)	**Present Disorders**	**Past Disorders**
ADHD, Combined Type	22	23
ADHD, Inattentive Type	1	0
ADHD, NOS	0	0
Conduct Disorder	1	0
ODD	19	21
Disruptive Behavior Disorder NOS	3	3
Generalized Anxiety Disorder	3	3
Separation Anxiety Disorder	2	4
Social Anxiety Disorder	1	1
Anxiety Disorder NOS	3	3
PTSD	0	1
Adjustment Disorder	0	2
Major Depressive Disorder	0	2
Depressive Disorder NOS	1	1
Enuresis	1	5
Specific Phobia	0	0
Eating Disorder NOS	0	0
Tourette's Disorder	1	1
HC Group (n=27)		
Enuresis	0	2
Specific Phobia	1	1
Eating Disorder NOS	0	1

Table 3

Paternal DSM-IV substance use disorders among high risk youth (n=23).

	# of Fathers Diagnosed	% of Fathers with Diagnosis
Alcohol Dependence	16	69.6
Alcohol Abuse	2	8.7
Cannabis Dependence	12	52.2
Cannabis Abuse	3	13.0
Cocaine Dependence	11	47.8
Hallucinogen Dependence	2	8.7
Opiate Dependence	6	26.1
Opiate Abuse	1	4.3
Sedative Dependence	2	8.7
Polysubstance Dependence	10	43.5

Number of SUD Diagnoses Per Individual	# of Individual Fathers	% of Total Fathers
1 SUD diagnosis	2	8.7
2 SUD diagnoses	3	13.0
3 or greater diagnoses (includes polysub.)	18	78.3

Table 4

Measures of performance on the BART task including winnings, reaction times, completed balloons and characteristics of won or lost balloon outcomes.

Total Winnings	Healthy Comparison		High Risk	
	$10.35 (± 0.48)		$11.51 (± 0.53)	
Reaction Times >5000 ms**	0.70 (± 0.99)		0.04 (± 0.21)	
Reaction Times of Inflate Trials (ms)	835.91 (± 53.47)		710.09 (± 43.99)	
Total Balloons Completed	20.40 (± 0.48)		20.39 (± 0.72)	
	Successful Inflations	Explosions	Successful Inflations	Explosions
Number of Balloon Outcomes	15.37 (± 0.75)	4.81 (± 0.34)	15.26 (± 0.94)	5.13 (± 0.38)
Inflations per Balloon	5.35 (± 0.15)	4.59 (± 0.15)	5.57 (± 0.17)	4.85 (± 0.21)
Minimum Number of Inflations	3.44 (± 0.23)	2.96 (± 0.20)	3.39 (± 0.27)	3.22 (± 0.20)
Maximum Number of Inflations	6.89 (± 0.20)	6.26 (± 0.27)	7.43 (± 0.22)	6.61 (± 0.31)
Reaction Times (ms)	770.69 (±66.23)*	727.85 (± 61.35)	554.82 (±38.31)*	634.68 (± 69.69)

* denotes group differences with a significance of $p<0.05$

** Number of instances of reaction times which were >5000 ms, across all participants in each group.

Table 5

Regions with significant group differences and interactions during the BART task *with* parametric modulation of probability of explosion modeled. Choice contrasts are Choose Win vs. Choose Inflate and outcome contrasts are Outcome Inflate vs. Outcome Explode. Cluster size is defined by the number of voxels. Coordinates are provided for the peak voxel in each cluster.

	BA	Peak F Value	Cluster Size	Talairach Coordinates		
				X	Y	Z
CHOICE CONTRASTS						
None						
OUTCOME CONTRASTS						
Main effect of Group						
R & L vmPFC	24/25	13.27	330	−1	11	−6
Group X Condition Interaction						
R Ventral Striatum/ACC	24/25	17.43	453	5	15	−4
R Inferior Frontal Gyrus/Anterior Insula	44/13	16.49	443	41	13	14

Abbreviations: BA= Broadman Area; R=right; L=left; vmPFC= ventromedial prefrontal cortex; ACC=anterior cingulate cortex

Table 6

Regions with significantly different activation between groups or group x condition interactions found during the BART task, *without* modeling parametric modulation ($p < .05$, corrected for multiple comparisons). Choice contrasts are Choose Win vs. Choose Inflate and outcome contrasts are Outcome Inflate vs. Outcome Explode. Cluster size is defined by the number of voxels. Coordinates are provided for the peak voxel in each cluster.

	BA	Peak F Value	Cluster Size	Talairach Coordinates		
				X	Y	Z
CHOICE CONTRASTS						
None						
OUTCOME CONTRASTS						
Main Effects of Group						
None						
Group X Condition Interaction						
L Parahippocampal Gyrus/Fusiform Gyrus/Occipital Cortex	20/37	28.21	2548	−27	−33	−20

Abbreviations: BA=Broadman Area; L=left