



Brain responses during delay discounting in youth at high-risk for substance use disorders

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ABSTRACT

Offspring of parents with substance use disorders (SUD) discount future rewards at a steeper rate on the monetary delay discounting task (DD) than typically developing youth. However, brain activation during DD has yet to be studied in drug naïve youth with a family history (FH) of SUD. Here, we investigate brain activation differences in high-risk youth during DD. We recruited substance naïve youth, aged 11–12, into three groups to compare brain activation during DD: (1) High-risk youth ($n = 35$) with a FH of SUD and externalizing psychiatric disorders, (2) psychiatric controls ($n = 25$) who had no FH of SUD, but with equivalent externalizing psychiatric disorders as high-risk youth, and (3) a healthy control group ($n = 24$) with no FH of SUD and minimal psychopathology. A whole-brain voxel wise analysis of the [Delay > Baseline], [Immediate > Baseline], and [Control > Baseline] contrasts identified functional regions of interest, from which extracted parameter estimates were tested for significant group differences. Relative to control youth, high-risk youth showed stronger activation in the left posterior insula and thalamus when making delayed choices, and stronger activation of the parahippocampal gyrus when making both delayed and control choices ($p_s < 0.05$). Activation in the left posterior insula negatively correlated with both subscales of the Emotion Regulation Checklist, and positively correlated with the Stroop interference effect ($p_s < 0.05$). Our findings suggest possible heritable SUD risk neural markers that distinguish drug naïve high-risk youth from psychiatric and healthy controls.

1. Introduction

A family history (FH) of substance use disorder (SUD) confers substantial risk to youth for developing a SUD themselves (Kendler et al., 1997). Prior work suggests that this heritable risk may be transmitted, at least in part, through externalizing traits (Kendler et al., 1997; Tarter et al., 2003) and impulsivity (Dougherty et al., 2014; Verdejo-García et al., 2008). These findings suggest common heritable causes in youths with a FH of SUD that begin to emerge during pre-adolescent brain development. While differences in impulsivity have been studied using behavioral delay discounting (DD) in pre-adolescent high-risk youth (Dougherty et al., 2014), DD has yet to be studied in this population using functional magnetic resonance imaging (fMRI). Investigating the neural basis of delay discounting in pre-adolescence, rather than

adolescence (Rodríguez-Moreno et al., 2021), makes it possible to assess whether brain function differences exist in high-risk youth prior to drug exposure, as many high-risk youth have experimented with substances by adolescence (Marmorstein et al., 2010).

Self-reported externalizing or disinhibitory traits exhibit behaviors that fall within the loosely-defined ‘impulsivity’ construct, e.g. “...the tendency to give in to urges, to act before thinking, to seek out excitement, and to have difficulty controlling one’s behavior” (NIH, 2020). While the broad impulsivity construct lacks precision (Strickland and Johnson, 2020), temporal discounting is a specific behavioral tendency (Yeh et al., 2021) within this impulsivity domain that is operationalized as the degree to which a reward is devalued as a function of delay (Ainslie, 1975). Temporal discounting behavior is assessed with DD tasks, and readily quantified using a series of binary choices between a

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smaller sooner (often immediate) versus a larger delayed reward (Ainslie, 1975). DD is stable over time (Kirby, 2009; Ohmura et al., 2006), across commodity type (Oberlin et al., 2021; Odum, 2011), reveals differences between various SUDs and controls (Amlung et al., 2017; MacKillop, 2013), longitudinally predicts later SUD (for review see Acheson et al., 2019; Mitchell, 2011), and tracks with FH of SUD (Dougherty et al., 2014; Rodriguez-Moreno et al., 2021). Steep DD is therefore a behavioral endophenotype that may elucidate causal mechanisms common to both impulsive behavior and SUD.

DD tasks activate the default mode, frontoparietal, salience, and reward network brain regions in healthy adults (for review see Frost and McNaughton, 2017), with similar patterns in typically developing youth (de Water et al., 2017; Hamilton et al., 2020). The only study to date that examined DD activation in youth FH positive for SUD found no differences compared to FH negative youth (Rodriguez-Moreno et al., 2021). While some of the regions implicated in DD are common to other decision-making and risk-taking tasks, effects of FH are mixed. For instance, the monetary incentive delay (MID) task elicits greater reward-related activation in the caudate (Andrews et al., 2011) and the putamen (Stice and Yokum, 2014), as well as executive control-related dorsolateral prefrontal cortex (dlPFC; Stice and Yokum, 2014) in FH positive relative to FH negative youth. However, FH negative relative to FH positive youth, show greater activation in salience and reward regions such as the insula (Andrews et al., 2011; Bjork et al., 2008), the anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC; Andrews et al., 2011), during risk-taking tasks such as the balloon analogue risk task (BART; Hulvershorn et al., 2015) and the Iowa Gambling Task (IGT; Acheson et al., 2009). The literature is similarly mixed regarding the nucleus accumbens (NAc), with some studies reporting no differences between FH positive and FH negative youth (Bjork et al., 2008; Müller et al., 2015; Yarosh et al., 2014), some finding greater activation in FH negative youth (Andrews et al., 2011), and others showing greater activation in FH positive youth (Hulvershorn et al., 2015). Interestingly, a recent neuroimaging meta-analysis focused on FH risk (Tervo-Clemmens et al., 2020) suggested that stronger striatal activation was associated with substance use risk (although note that replication in the right putamen was driven by reward related tasks, rather than tests of cognitive control).

At least three gaps persist in the current neuroimaging studies of SUD risk germane to reward decision-making. First, the majority of research to-date was conducted in youth that have already initiated substance use (Acheson et al., 2009; Andrews et al., 2011; Müller et al., 2015; Rodriguez-Moreno et al., 2021; Stice and Yokum, 2014; Yarosh et al., 2014), yielding data potentially affected by substance exposure (Boileau et al., 2006). Second, studies' treatment of psychiatric comorbidity may be suboptimal, with exclusion (Acheson et al., 2009; Andrews et al., 2011; Yarosh et al., 2014), uneven representation (Hulvershorn et al., 2015), or omitted reporting (Müller et al., 2015; Rodriguez-Moreno et al., 2021; Stice and Yokum, 2014) making conclusions about real-world populations unreliable. The high comorbidity of SUDs and externalizing disorders (Krueger et al., 2002) ideally requires the samples to be equally enriched in externalizing disorders to ensure externally valid interpretations. Third, the nature of neural activation during DD is yet unknown in completely drug-naïve FH positive pre-adolescent youth and given the strength of heritable predictive risk represent critical data to inform the field.

To address these gaps we recruited substance naïve, pre-adolescent youth participants into three groups to compare their DD task performance and brain activation: (1) high-risk youth with a FH of SUD and diagnosed high-risk psychiatric condition (Tarter et al., 2003), (2) psychiatric controls (PC) with no FH of SUD, but equivalent numbers and severity of disruptive behavior diagnoses as the high-risk group to investigate activation differences unique to a FH of SUD, and (3) healthy controls (HC) with minimal psychopathology and no FH of SUD.

We employed a whole-brain, agnostic approach to investigate group differences in activation during a DD task for both immediate and

delayed choices, and control trials. Activation to each choice type was examined separately due to longer response times for delayed, relative to immediate choices and control trials. Consistent with greater frontal inhibitory demands and previous FH risk literature, we hypothesized that high-risk youth would show stronger engagement of the dlPFC and lesser engagement of the ACC in comparison to both control groups during both immediate and delayed choices. We examined associations in regions exhibiting group differences with emotion regulation and lability, as deficits in these categories are associated with positive drug expectancies in drug-naïve youth (Dir et al., 2016). Additionally, in regions exhibiting group differences we also investigated relationships with the Stroop interference effect, which is known to be associated with a FH of SUD (Lovallo et al., 2006). Last, we performed an exploratory region-of-interest (ROI) analysis of the dorsal and ventral striatal regions implicated in delay discounting during the decision-making phase, as previous high-risk literature is inconclusive about striatal functioning in the context of reward anticipation and outcome.

2. Methods

2.1. Participants

Eighty-four right-handed 11–12-year-old male and female children were enrolled in a 5-year longitudinal study with usable behavioral and imaging DD data. High-risk participants' biological father and another first or second-degree relative had a past or present SUD (excepting isolated tobacco or alcohol use disorders). High-risk participants additionally met DSM-5 (American Psychological Association, 2013) criteria for ADHD (any subtype), plus a disruptive behavior disorder, defined here as conduct disorder, oppositional defiant disorder, or a disruptive behavior disorder, other specified. PC participants met DSM-5 criteria for ADHD (any subtype) plus a disruptive behavior disorder and had no first-degree relatives and no more than two second degree relatives with SUDs. HC participants lacked any DSM-5 psychiatric diagnoses (except specific phobias, enuresis, encopresis, and learning disorders), and had no first-degree relatives and no more than two second degree relatives with SUDs. Recruitment attempted to match groups on age, race, sex, IQ, & SES. Exclusion criteria included reporting or testing positive for any recreational drug use (prescription or illicit drugs, alcohol, or nicotine) at baseline assessment, reported *in utero* exposure to drugs or alcohol; youth diagnosed with bipolar disorder, psychotic symptoms, autism or current major depressive disorder; pssycho pharmacologic treatment within the past two weeks (except for psychostimulants—though these were withheld for interview and scan days); history of neurological problems; full scale IQ below 80; debilitating medical conditions; or MRI contraindications. Participants were recruited from community and online advertisements as well as from psychiatric clinics and were proficient in English. All procedures were conducted on an urban mid-western medical school campus and approved by Indiana University's Institutional Review Board.

2.2. Assessment

Parents completed a phone screen with a research technician to determine their child's eligibility. If qualified, at least one parent or guardian and the adolescent provided written consent/assent during the in-person, baseline assessment. A rapid urine toxicology screen (Uritox Medical) tested for illicit drugs (methamphetamine, amphetamine, benzodiazepines, cocaine, opiates, and cannabis), and youth were breathalyzed to test for alcohol. To verify drug abstinence history, the substance use portion of the Drug Use Screening Inventory (Kirisci et al., 1995) was given to each adolescent privately.

A trained adolescent mental health clinician completed the K-SADS-PL semi-structured interview, modified for DSM-5 (Kaufman et al., 1997), with both the parent and adolescent to determine present and lifetime psychiatric diagnoses (Table 1). Diagnoses were confirmed

Table 1
Participant characteristics and psychiatric diagnoses.

(A) Participant characteristics						
	High-Risk (HR; n = 35)	Psychiatric Controls (PC; n = 25)	Healthy Controls (HC; n = 24)	Significance		
Age	11.9 ± 0.5	11.9 ± 0.6	12.1 ± 0.6	p = 0.42		
Male (%)	68.6	72.0	66.7	p = 0.92		
Race	15 W; 6 M; 13 AA	15 W; 5 M; 5 AA	10 W; 4 M; 10 AA	p = 0.59		
Ethnicity	1HL; 34 NHL	25 NHL	25 NHL			
IQ	105.8 ± 14.4	109.8 ± 16.3	108.0 ± 13.5	p = 0.59		
SES ^a	4.3 ± 1.4	4.0 ± 1.1	3.9 ± 1.1	p = 0.47		
PDS ^b	1.9 ± 0.8	1.9 ± 0.9	2.0 ± 0.7	p = 0.92		
CTES ^b	2.3 ± 1.4	2.1 ± 1.4	1.4 ± 0.9	p = 0.04*		
(B) DSM Diagnoses						
	Current Disorders			Past Disorders		
	HR (n = 35)	PC (n = 25)	HC (n = 24)	HR (n = 35)	PC (n = 25)	HC (n = 24)
ADHD	35 (100%)	25 (100%)	0	35 (100%)	25 (100%)	0
CD	2 (6%)	1 (3%)	0	2 (6%)	1 (3%)	0
ODD	27 (77%)	16 (46%)	0	27 (77%)	16 (46%)	0
DBD	5 (14%)	8 (23%)	0	5 (14%)	8 (23%)	0
Anxiety Disorders	16 (45%)	9 (36%)	2 (8%)	17 (49%)	9 (36%)	2 (8%)
Mood Disorders	0	1 (4%)	0	3 (9%)	2 (8%)	0
Other	6 (17%)	2 (8%)	0	15 (43%)	4 (16%)	0

(A) Details participant characteristics, (B) details diagnoses for all groups from the K-SADS-PL semi-structured interview modified for the DSM-5. (A) W – White; M – Mixed Race; AA – African American; HL – Hispanic or Latino; NHL – not Hispanic or Latino; PDS – Pubertal Development Scale; CTES – Childhood Traumatic Events Scale. Means are ± SD. ^aSocioeconomic status (SES) is measured by parental level of education: 1 = High school diploma or equivalent, 2 = Some college, 3 = Associate's degree/vocational training, 4 = Bachelor's degree, 5 = Some graduate/professional school, 6 = Completed graduate/professional school. ^bData missing for 5 participants. * $p < 0.05$ (B) DSM – Diagnostic Statistical Manual; ADHD – attention deficit hyperactivity disorder; CD – conduct disorder; ODD – oppositional defiant disorder; DBD – disruptive behavior disorder; anxiety disorders = adjusting disorder, adjusting disorder with disturbance of conduct, generalized anxiety, separation anxiety, anxiety not otherwise specified, obsessive compulsive disorder, post-traumatic stress disorder, acute stress disorder, and selective mutism; mood disorders = disruptive mood dysregulation disorder, major depressive disorder, and depressive disorder not otherwise specified; other = enuresis, encopresis, Tourette's and tic disorder.

through a consensus diagnostic process with a team of clinicians. Parents completed the Emotion Regulation Checklist (ERC; Shields and Cicchetti, 1997), a 24-item scale with two subscales measuring the adolescent's emotion regulation (Cronbach's $\alpha = 0.90$) and lability/negativity (Cronbach's $\alpha = 0.83$). Lability/negativity was reverse scored, and mean scores were calculated for each subscale. Parents also completed the Childhood Traumatic Events Scale (CTES) to determine whether the child had experienced any of six potentially traumatic events (death of a family member or close friend, parental divorce or separation, sexual abuse, victim of violence, having been extremely ill or injured, and other major upheaval) in childhood (Pennebaker and Susman, 1988) and the Pubertal Development Scale (Carskadon and Acebo, 1993) to assess the youth's pubertal status. Additionally, parents completed the Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994) to assess paternal SUD (Table 2). If the father was unavailable for screening, the non-patient edition was given to the available parent or guardian regarding the father. Current maternal drug use was not exclusionary but was not sought out during

Table 2
Paternal substance use disorders.

High-risk Paternal DSM-5 Substance Use Disorder (SUD) Diagnoses ^a			
	Mild	Moderate	Severe
Alcohol	5	6	17
Cannabis	11	6	13
Methamphetamine	4	0	3
Cocaine	6	1	5
Opiate	1	0	2
Sedative	4	2	2
Hallucinogen	4	0	1
# of SUD diagnoses per individual	# of Fathers		
1 diagnosis	6		
2 diagnoses	11		
3 diagnoses	18		

^aPaternal substance use disorder diagnoses for the high-risk group from the Semi-Structured Assessment for the Genetics of Alcoholism.

recruitment to limit the probability of *in utero* drug exposure. Reported drug use during pregnancy at screening was exclusionary, however during study procedures *in utero* exposure was reported for five participants. Additionally, youth were IQ screened using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

2.3. Behavioral tasks

Stroop test. To assess cognitive control of behavior, each adolescent completed the Stroop Color-Word Test (Unsworth et al., 2012) that included 75 trials (67% of trials neutral and 33% incongruent). Neutral trials required the adolescent to correctly select the color of the displayed "X" (from red, green, blue). Incongruent trials required the adolescent to correctly select the color of color-name words presented in other colors (e.g. the word RED presented in blue font). Executive function was assessed with the Stroop interference effect (MacLeod, 1991)—i.e. the difference in accuracy between the neutral and incongruent trials.

fMRI delay discounting task. Before beginning the DD task, participants were instructed to make choices that most accurately reflected their true preference. Each choice trial displayed, "Which do you prefer?" with an immediate and a delayed option on either (randomized) side of the screen, e.g., "\$10.00 after 20 days OR \$3.34 now" (Fig. 1). Due to time constraints, the fMRI delay discounting task procedures changed part way through data collection. For initial participants ($n = 21$), a pre-scan baseline adjusting amount task was given to derive indifference points for \$10 at delays of 2 days, 1 week, 1 month, 6 months, 1 year, & 5 years using a staircase procedure (Du et al., 2002; Oberlin et al., 2015). Nonlinear regression derived the fitted parameter k (Mazur, 1987), which was then used to parameterize the in-scanner task. In-scanner task choices were biased to promote equal trial numbers (bias: 40–50% above and below the indifference curve for immediate- and delay-biased trials, respectively), with 15 trials of each type. Ten additional control trials required identifying the larger of two monetary amounts and controlled for visual presentation and motor response. The task created for the median discounting rate (from the initial $n = 21$) was

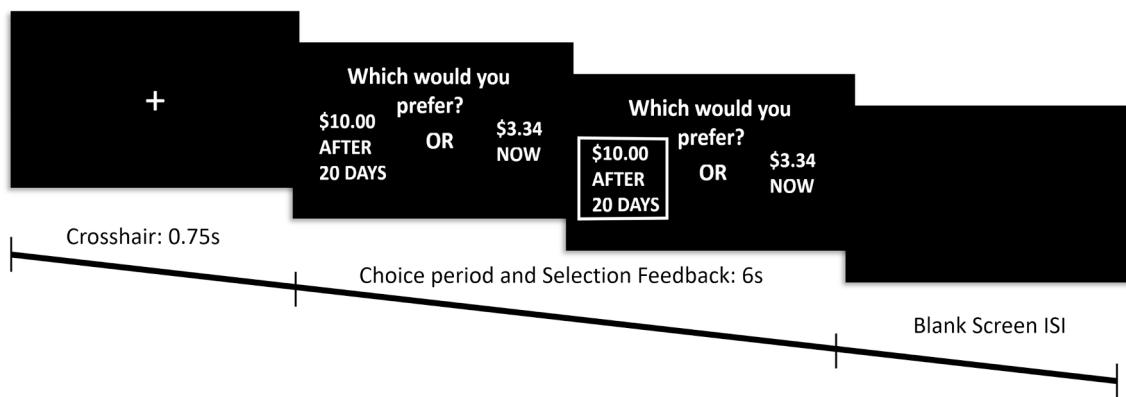


Fig. 1. Schematic representation of a single choice trial presented during the fMRI DD task. Mean intertrial interval is 11 s. Crosshair indicates the beginning of each trial, and the participant then has up to 6 s to make a choice with feedback indication up to 1 s. Blank screen mean ISI = 4.25 s, with 1 s jitter. ISI = interstimulus interval.

presented with randomized trials for the remaining participants ($n = 63$). Participants performed the DD task in two consecutive scans (runs). Since out-of-scanner DD data were not collected for all participants, we analyzed behavioral DD data from the in-scanner tasks using an immediate choice ratio (i.e., immediate choices/total choices, excepting omissions (Benningfield et al., 2014; Ersner-Hershfield et al., 2009; Magen et al., 2008)). Since the task was optimized to promote an immediate choice ratio of 0.5 for the initial ($n = 21$) participants, before using immediate choice ratio as a measure of behavior for group analyses, we confirmed immediate choice ratios did not differ between the initial 21 (0.40 ± 0.24) and remaining 63 participants (0.44 ± 0.23 ; $p = 0.50$).

2.4. Image acquisition

Imaging was performed on a Siemens 3 T Prisma (Erlangen, Germany) MRI scanner using a 32-channel head coil array. During two delay discounting scans (7:25 each) 365 whole-brain blood oxygenation level dependent (BOLD) contrast volumes were acquired using a multiband (MB) echo planar imaging (EPI) sequence (Center for Magnetic Resonance Research at the University of Minnesota, gradient echo, repetition/echo time TR/TE = 1200/29 ms, flip angle 65° , field-of-view 220×220 mm, matrix 88×88 , 54 axial slices, $2.5 \times 2.5 \times 2.5$ mm³ voxels, MB slice acceleration factor = 3) (Smith et al., 2013; Xu et al., 2013). BOLD scans were preceded by two short (16 sec each) spin echo EPI field mapping scans to correct for field inhomogeneity (TR/TE = 1560/49.8 ms; 5 A-P and 5P-A phase direction volumes) with the same coverage, voxel size, and slice acceleration as the BOLD EPI acquisition. A high resolution, T1-weighted, anatomic volume (3D magnetization prepared rapid gradient echo (MP-RAGE); 5:12 min; 176 sagittal slices; $1.05 \times 1.05 \times 1.2$ mm³ voxels; GRAPPA R = 2 acceleration) was acquired at the beginning of the imaging session.

2.5. Image preprocessing

Functional images of each participant were preprocessed with FMRIB Software Library (FSL version 6.0) (Jenkinson et al., 2012), including unwarping with *topup/applytopup* (Andersson et al., 2003; Smith et al., 2013) that utilized spin echo field mapping scans, motion correction with *mcfirt* (Jenkinson et al., 2002), brain extraction with *bet* (Smith, 2002), registration to participant's T1 image and MNI152 standard space, and 6 mm FWHM Gaussian filter spatial smoothing. FSL's MELODIC version 3.15 automatically estimated and retained optimal number of independent components for each scan (82.0 ± 2.6) across all scans in the sample. Scans with a high mean absolute (>2 mm) or relative (>0.5 mm) head motion warning from MELODIC were excluded from further analyses, while maintaining blindness to group membership. Groups included in the final analyses did not differ in

motion levels as indexed by median frame displacement generated by *fsl_motion_outliers* ($p = 0.16$). To ensure robust processing, we performed independent component analysis (ICA)-based data cleaning, following the recommendation of Eklund et al. (2019a). We employed an unsupervised ICA-AROMA (Pruim et al., 2015) classifier, which when applied to clinical population data performed similarly (Carone et al., 2017) to the manually-trained ICA-FIX (Salimi-Khorshidi et al., 2014). Denoised images generated by ICA-AROMA were projected into MNI space, interpolated to 2 mm isotropic voxels, and analyzed in Statistical Parametric Mapping 12 (SPM12) using voxel-level inferences that are reported to achieve a nominal false positive rate (Eklund et al., 2016) (for more details see section 2.6).

2.6. Statistical analyses

Behavior. To characterize DD behavior during fMRI, we calculated an immediate choice ratio (see section 2.3) for each participant. We tested for group differences using a mixed analysis of variance (ANOVA), with scan as a within subject factor and group as a between subject factor. To investigate possible differences in reaction time (RT), we employed a mixed ANOVA with choice type and scan as within participant factors, and group as a between participant factor. Greenhouse-Geisser corrections were applied for violations of sphericity.

Imaging. Individual-level responses to immediate and delayed choices and control trials were modeled using the canonical hemodynamic response function (HRF) in SPM12. To capture the decision-making period, we modeled the HRF of each trial (mean inter-trial interval = 11 s; see Fig. 1) using the epoch starting 400 ms after choice presentation (accounting for semantic comprehension (Hagoort et al., 2004)) and 50 ms before the response (to minimize motor signal (Pfefferbaum et al., 1985)). An autoregressive AR(1) model accounted for serial correlations with a high-pass filter set to (1/128 Hz) to remove low-frequency noise. Choice type (immediate, delayed) and control trials compared to implicit baseline, (i.e., [Immediate > BL], [Delayed > BL], [Control > BL]) contrast images of each participant were entered into a factorial SPM model, with choice type as a dependent factor with three levels. To maximize detection of brain areas involved in inter-temporal choice we first identified areas of significant activation (voxel-level significance, corrected for whole-brain family-wise error (FWE), $p_{FWE} < 0.01$, $k = 50$) from the [Immediate > BL], [Delayed > BL], and [Control > BL] contrasts. A stricter FWE value of 0.01 was used because one-sided t-tests (which are the default in SPM (Eklund et al., 2019b)) yield suboptimal false positive rate control (i.e. the actual family-wise error (FWE) rate in one-sided test ($p < 0.05$) is 10%), and therefore, require a multiple comparisons correction (Chen et al., 2019). A more stringent $p_{FWE} = 0.01$ threshold maintains the overall family-wise false positive error rate below 5%. Next, we extracted mean regression parameter estimates from each identified functional ROI (Fig. 2) using

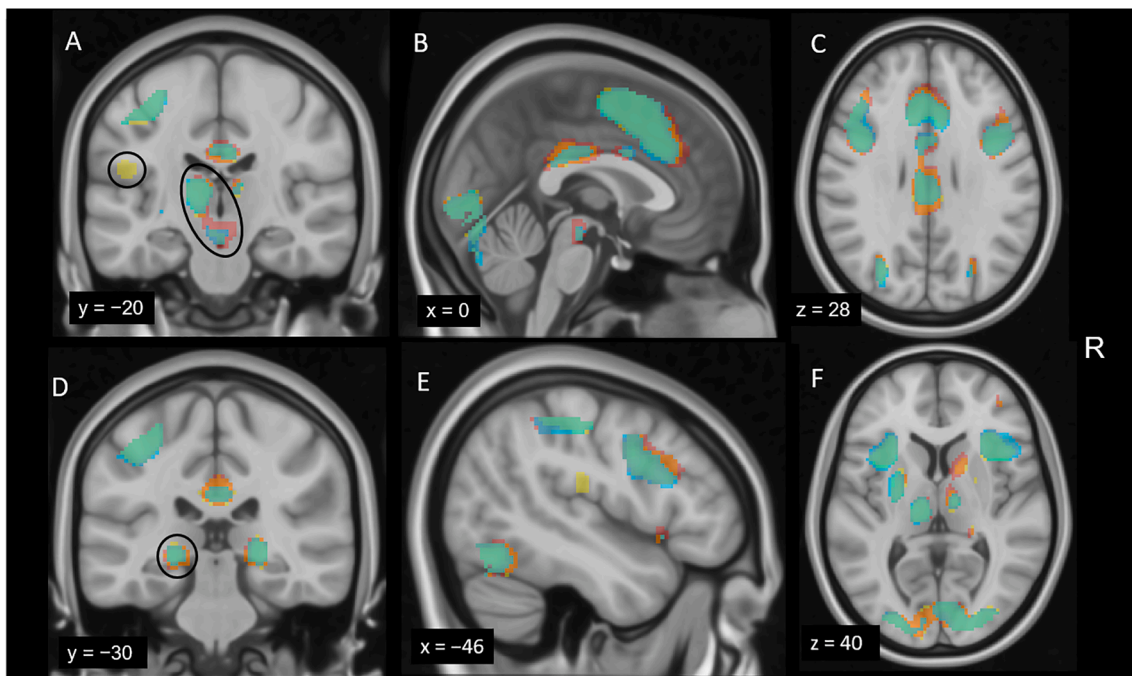


Fig. 2. Intertemporal choice regions. Brain areas that respond to delayed, immediate, and control choices (yellow, red, and cyan, respectively) largely overlap (green). The three regions where risk groups of interest differ are circled on the coronal views (A, D; see also Fig. 3). Other prominent choice elicited activations where no group differences were detected include visual (B, E, F), premotor/cingulate cortex (B, C), frontoparietal/anterior insula (C, F), and striatal (F) areas. Displayed at voxel level significance (peak $p_{FWE} < 0.01$, $k > 50$), family-wise error-corrected for whole-brain multiple comparisons; see Table 3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

MarsBar (Brett et al., 2002). Separate MANCOVAs were run in SPSS (v26; IBM) for each contrast (immediate, delayed, and control) to investigate differences between the three groups, and extracted functional ROIs from each contrast were included as the dependent variables in their respective analysis. Striatal functioning was investigated using ROIs from a subcortical atlas (Scale-III parcellation; Tian et al., 2020), see Inline Supplementary Figure 1. Extracted mean parameter estimates for each striatal ROI were also tested in a MANCOVA for differences between the three groups. Biological sex was used as a covariate in all SPSS group difference analyses. Results were summarized as statistically significant when the p -values were < 0.05 . No correction was applied for the number of MANOVAs ran, as each test corresponded to a different condition (see section 4.1). Regions yielding group differences were then tested for associations with cognitive control of behavior and emotion regulation as measured by the Stroop task and ERC, respectively.

3. Results

3.1. Sample characteristics

A total of 152 right-handed youth completed the imaging protocol. Forty-eight participants were excluded from analyses due to strongly biased choices during the DD task (i.e., selecting less than three choices in either the immediate or delayed conditions, yielding underpowered conditions) and 20 participants were excluded for excessive head motion (flagged by MELODIC), for a final sample of 84. Excluded participants did not differ in group membership ($p = 0.22$). There were no significant group differences in age, gender, race, IQ, socioeconomic status (as indexed by parental level of education), pubertal development, or head motion (assessed using frame displacement metric), all p s > 0.16 (Table 1). Groups differed based on the Childhood Traumatic Events Scale (CTES; $F(2,76) = 3.27$, $p = 0.04$, $\eta_p^2 = 0.08$), and Bonferroni corrected post-hoc tests revealed high-risk youth experienced more traumatic events than healthy control youth ($p = 0.05$). Clinical

sample characteristics are detailed in Table 1, and paternal SUDs are detailed in Table 2.

3.2. Delay discounting behavior

Groups did not differ in immediate choice ratio, ($p = 0.99$). There was a main effect of scan, such that participants made more immediate choices in the first scan compared to the second ($F(1,77) = 10.10$, $p = 0.002$; Wilk's $\Lambda = 0.88$; $\eta_p^2 = 0.12$), but there was no interaction effect of group and scan. Groups did not differ in RT, $p = 0.98$. There was a main effect of choice type on RT ($F(1.76,119.45) = 70.00$, $p < 0.001$; $\eta_p^2 = 0.51$); as well as a scan by choice type interaction ($F(2,136) = 5.150$, $p = 0.007$; $\eta_p^2 = 0.07$). Delayed choice RTs were longer relative to immediate, with both longer than control, ($ps < 0.02$), with means and standard deviations (SD) of 2.43 ± 0.48 s, 2.05 ± 0.52 s, 1.97 ± 0.34 s, respectively. RTs to immediate ($p = 0.04$) and control ($p = 0.03$) trials were significantly faster in scan two than scan one.

3.3. Whole-brain findings

Delayed, immediate, and control choices elicited activation in 14, 10, and 11 brain regions, respectively, mainly in the midline default mode, frontoparietal, and salience networks (Fig. 2, Table 3). The brain regions involved in both choice types largely overlapped, except the left posterior insular cortex (PIC), which was recruited solely during delayed choices. When directly comparing [Delayed $>$ Immediate] and [Immediate $>$ Delayed], no areas satisfied the voxel-wise $p_{FWE} < 0.01$ criterion across the whole brain.

3.4. Group differences in activation

We detected group differences in the [Delayed $>$ BL] contrast ($F(28,134) = 1.70$, $p = 0.024$; Wilk's $\Lambda = 0.54$; $\eta_p^2 = 0.26$). Groups differed in the left posterior insula ($F(2,80) = 5.25$, $p = 0.007$; Fig. 3A), left thalamus ($F(2,80) = 3.95$, $p = 0.023$; Fig. 3B), and left parahippocampal

Table 3
Significant activation clusters by contrast.

Brain Regions by contrast	Cluster size	Peak voxel	Peak voxel	MNI Coordinates (mm)		
				<i>k</i>	<i>p</i> _{FWE}	<i>Z</i>
[Delayed > Baseline]						
Visual Cortex	8167	<0.001	>8	-24	-90	-12
		<0.001	>8	18	-92	-4
		<0.001	>8	20	-94	4
SMC	2772	<0.001	>8	-2	10	50
		<0.001	>8	6	24	34
L PrG	598	<0.001	>8	-38	-24	56
L PrG	756	<0.001	>8	-42	0	34
L MFG		0.001	5.83	-38	24	20
L PrG		0.003	5.35	-34	-6	50
L PHG	168	<0.001	>8	-20	-32	-4
R PHG	215	<0.001	>8	22	-32	-2
L Thalamus	318	<0.001	>8	-10	-20	8
L VTA	<0.001	5.72	>8	-4	-22	-12
R AIC	1189	<0.001	>8	36	18	-2
R Putamen		<0.001	>8	28	8	-2
R MFG	1021	<0.001	>8	44	32	22
R PrG		<0.001	>8	42	4	32
R MFG		<0.001	6.39	40	46	10
PCC	604	<0.001	>8	4	-32	26
MCC		<0.001	>8	6	-20	28
MCC		<0.001	6.80	6	4	28
L AIC	1341	<0.001	>8	-32	16	4
L Putamen		<0.001	>8	-28	-4	-2
R Thalamus	132	<0.001	>8	10	-14	8
L PIC	62	<0.001	6.70	-46	-22	20
R Caudate	86	<0.001	6.41	14	6	8
[Immediate > Baseline]						
Visual Cortex	8279	<0.001	>8	-24	-90	-12
		<0.001	>8	-26	-92	-4
		<0.001	>8	-18	-96	-4
SMC	2830	<0.001	>8	-2	12	50
ACC		<0.001	>8	6	26	34
L PrG	596	<0.001	>8	-38	-24	56
L SMG		<0.001	7.62	-46	-38	-46
L PrG	955	<0.001	>8	-38	6	28
L IFG		<0.001	6.44	-48	20	26
L PrG		<0.001	6.11	-40	0	50
R AIC	2717	<0.001	>8	36	18	-2
R MFG		<0.001	>8	46	30	24
R PrG		<0.001	>8	44	8	30
R PHG	248	<0.001	>8	22	-32	-2
L PHG	199	<0.001	>8	-20	-32	-4
L Thalamus	493	<0.001	>8	-10	-20	8
VTA		<0.001	7.10	-2	-20	-12
SN		<0.001	6.76	-8	-22	-4
L AIC	1328	<0.001	>8	-34	16	0
L Putamen		<0.001	>8	-28	-4	-2
L Caudate		0.001	5.55	-16	0	12
PCC	753	<0.001	>8	4	-30	28
MCC		<0.001	>8	6	-18	28
MCC		<0.001	7.50	6	6	28
[Control > Baseline]						
L PrG	3178	<0.001	>8	-38	-24	56
L Putamen		<0.001	>8	-28	-4	-2
L AIC		<0.001	>8	-34	14	2
SMC	2630	<0.001	>8	-2	6	52
ACC		<0.001	>8	6	24	32
ACC		<0.001	>8	-6	20	32
Visual Cortex	7994	<0.001	>8	-28	-88	-12
		<0.001	>8	-24	-92	-6
		<0.001	>8	30	-84	-8
L Thalamus	380	<0.001	>8	-10	-20	8
SN		<0.001	6.41	-6	-26	-10
VTA		<0.001	6.04	0	-20	-14
R AIC	2462	<0.001	>8	32	22	-4
		<0.001	>8	40	16	-2
R PrG		<0.001	>8	42	4	32
R PHG	139	<0.001	>8	22	-30	-2
L PHG	91	<0.001	>8	-20	-32	-4
MCC	92	<0.001	7.06	4	6	28

Table 3 (continued)

Brain Regions by contrast	Cluster size	Peak voxel	Peak voxel	MNI Coordinates (mm)		
				<i>k</i>	<i>p</i> _{FWE}	<i>Z</i>
MCC	261	<0.001	7.61	6	-18	28
PCC		<0.001	6.65	-2	-28	28
R Thalamus	123	<0.001	7.51	10	-16	10
R Caudate		0.001	5.50	12	0	10
R MFG	91	<0.001	5.98	32	48	14
		0.003	5.33	32	46	24

Peak voxel-level significance ($p_{FWE} < 0.01, k > 50$), family-wise error corrected for whole-brain multiple comparisons. Secondary peaks are indented and regions displaying group differences are bolded. k = cluster size in number of voxels, p_{FWE} = corrected statistical significance, Z = standardized statistic based on the normal distribution, and MNI (x, y, z) = Montreal Neurological Institute coordinates. Anatomical region abbreviations: SMC – supplementary motor cortex; AIC – anterior insular cortex; PCG – precentral gyrus; Thal – thalamus; VTA – ventral tegmental area; SN – substantia nigra; PHG – parahippocampal gyrus; PCC – posterior cingulate cortex; SPL – superior parietal lobule; PIC – posterior insular cortex; SMG – supramarginal gyrus; MCC – middle cingulate gyrus.

gyrus (PHG; $F(2,80) = 3.74, p = 0.028$; Fig. 3C). High-risk participants showed more activation than the healthy control participants in the left PIC and left thalamus ($p = 0.003$ and $p = 0.018$, respectively). The high-risk group also showed significantly higher activation in the left PHG in comparison to the psychiatric control participants ($p = 0.046$). There were no significant group differences in the [Immediate > BL] contrast ($ps > 0.23$). Finally, group differences were also present in the [Control > BL] contrast ($F(22,140) = 1.67, p = 0.041$; Wilk's $\Lambda = 0.63$; $\eta_p^2 = 0.21$). Similar to our [Delayed > BL] finding, the left PHG differentiated the groups ($F(2,80) = 3.83, p = 0.026$; Fig. 3D), and again, the high-risk group produced stronger activation than the psychiatric control participants ($p = 0.041$). Adding the CTES score as a covariate to MANOVA analyses yielded qualitatively similar results ($ps < 0.03$).

3.5. Correlations in regions with group differences

3.5.1. Emotion Regulation Checklist (ERC)

Groups differed in both the emotion regulation ($F(2,81) = 4.63, p < 0.001$) and lability/negativity ($F(2,81) = 15.14, p < 0.001$) subscales of the ERC. Pairwise comparisons revealed that both the high-risk and psychiatric control participants had poorer regulation of their emotions than the healthy control participants ($ps < 0.001$; see Inline Supplementary Figure 2). The [Delayed > BL] activation in the left PIC was negatively associated with emotion regulation ($r(84) = -0.24, p = 0.04$; Fig. 3E) and emotional lability/negativity ($r(84) = -0.24, p = 0.04$; Fig. 3F) subscales of the ERC. Additionally, [Delayed > BL] activation in the left thalamus showed a trend-level negative association with the lability/negativity ($p = 0.06$; see Inline Supplementary Figure 3) subscale of the ERC.

Stroop task. There were no group differences in the Stroop interference effect ($p = 0.20$; see Inline Supplementary Figure 4). The [Delayed > BL] activation in the left PIC was positively associated with Stroop interference ($r(84) = 0.25, p = 0.04$; Fig. 3G). Due to a prominent outlier (Fig. 3G), we also applied Spearman's correlation ($r_s = 0.308$; $p = 0.007$).

3.6. Striatal region of interest findings

Mean regression parameter estimates extracted from the right and left caudate, putamen, and nucleus accumbens showed no group differences ($ps > 0.42$; see Inline Supplementary Figure 5) for the [Delayed > BL, Immediate > BL, and Control > BL] contrasts.

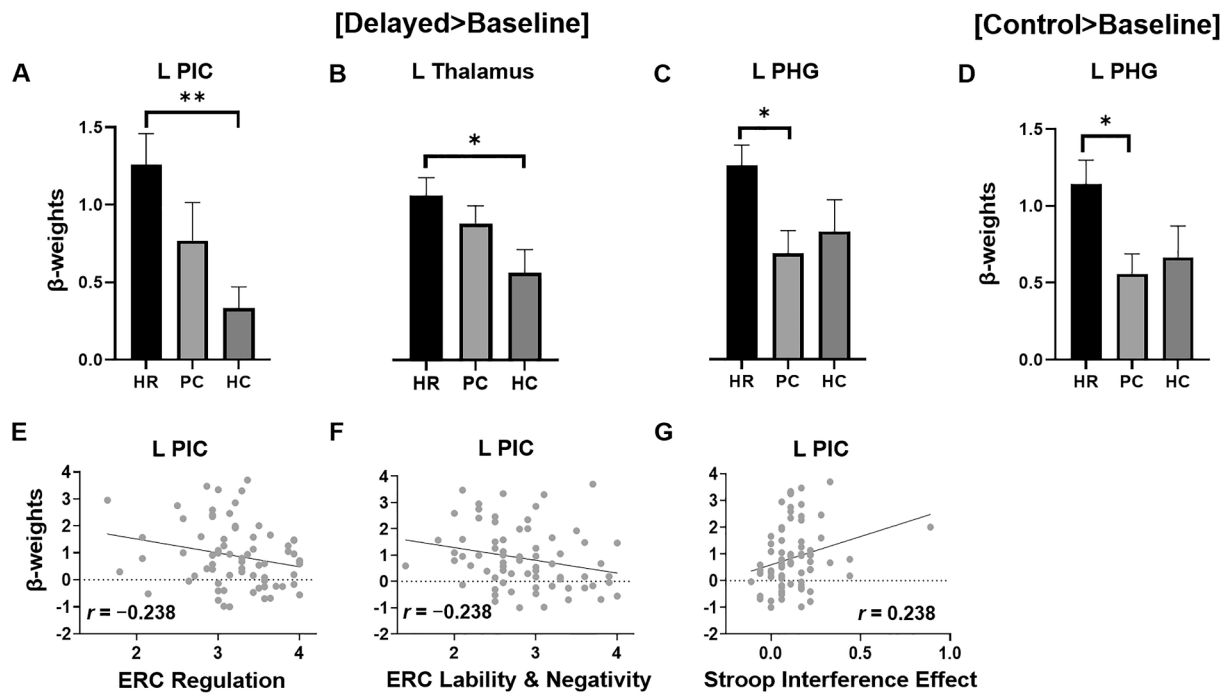


Fig. 3. Top row: Group differences between high-risk (HR) and healthy controls (HC) were observed in the [Delayed > Baseline] contrast in the (A) left posterior insular cortex (PIC) and (B) left thalamus. HR and psychiatric controls (PC) differed in the left parahippocampal gyrus (PHG) in the (C) [Delayed > Baseline] and (D) [Control > Baseline] contrasts. Bottom row: The left posterior insular cortex activation in the [Delayed > Baseline] contrast is associated with (E) the emotion regulation subscale of the Emotion Regulation Checklist (ERC) ($p = 0.04$), (F) the liability and negativity subscale of the ERC ($p = 0.04$) and (G) the Stroop interference effect ($p = 0.04$), Spearman's correlation ($p = 0.007$). $*p < 0.05$, $**p < 0.01$.

4. Discussion

This study sought to examine neural underpinnings of temporal discounting in drug naïve, pre-adolescent youth varying in SUD risk. Our 11–12 year old participants recruited regions primarily within the frontoparietal and salience networks—with some posterior default mode network—similar to what has been reported for adults during delay discounting (for review see Frost and McNaughton, 2017). Comparing with previous findings in adults (Wittmann et al., 2007), we detected posterior insula activation by delayed choices in youth. While brain regions engaged by the DD task were largely similar across groups, stronger activations in the left posterior insular cortex (PIC), parahippocampal gyrus (PHG), and thalamic regions of high-risk youth (when choosing delayed rewards) suggest heritable addiction-relevant brain mechanisms that exist prior to drug use. We found no group differences in DD behavior or striatal functioning.

The PIC is involved in encoding time (Wittmann et al., 2010; Wittmann et al., 2011), specifically the duration of an interval. Our findings resemble prior work, which shows the PIC specifically activating during delayed reward selection (Wittmann et al., 2007). The activation pattern in the PIC during delayed choice was high-risk > psychiatric control > healthy control, suggesting an additive marker for risk, with the highest risk associated with the most activation in this region (although note that the difference between high-risk and psychiatric control did not reach statistical significance).

The posterior and anterior insula are heavily interconnected, and together process incoming physiological data to derive interoceptive states (Craig, 2003; Nomi et al., 2016). Specifically the left PIC, but not the right, responds to emotional valence, with negative emotions eliciting greater PIC activation than positive emotions (Duerden et al., 2013). An intriguing possibility in the current findings is that the left PIC's activation during delayed reward choice signals the punishing aspect of delay. Indeed, we found that activation in the left PIC correlated with reduced emotional regulation and increased liability/

negativity. Emotional liability/negativity may indicate sensitivity to affective environmental cues, with greater sensitivity scaling with heightened emotional and physiological responses to challenging situations (Kim-Spoon et al., 2013; Pietromonaco and Barrett, 2009). Time perception arguably emerges from the progression of changing emotional and visceral states, which are processed in the PIC (Craig, 2009a; Craig, 2009b). Delayed choices produced longer reaction times in the present sample, likely indicating that these trials were more “challenging,” and therefore eliciting a stronger emotional response to the challenge of delayed trials in those with increased liability/negativity.

Additionally, activation in the left PIC correlated with Stroop interference, such that stronger activation corresponded with greater impairment. Left PIC activation is unique to both Stroop and Word-Oddball (rarely occurring words) interference (Melcher and Gruber, 2006), and language processing (Ardila et al., 2014; Chang et al., 2013). Our findings are consistent with greater PIC engagement for overcoming the effects of attentional interference.

High-risk youth also elicited stronger activation than healthy controls in the left thalamus with the peak effect in the mediodorsal portion. The mediodorsal thalamus plays an important role in goal-directed behaviors (Parnaudeau et al., 2015) and is part of a decision-monitoring network during tasks to ensure alignment with overall task goals (Dosenbach et al., 2008). Furthermore, it is bidirectionally connected with the medial PFC, OFC, and lateral PFC (Huang et al., 2018)—regions mediating reward valuation. The mediodorsal thalamus receives input from the striatum via pathways that both directly disinhibit and indirectly inhibit (indirect pathway) thalamic signaling to the cortex, which then provides positive feedback to the striatum (Haber and McFarland, 2001). As such, it is part of a cortico-striatal-thalamo-cortical circuit that mediates higher-order processes such as valuation/motivation and cognitive control (Aron, 2007; Haber and Knutson, 2010; Huang et al., 2018). Thus, stronger recruitment of the mediodorsal thalamus during the delayed choice in the high-risk group may indicate greater cognitive

effort expenditure to maintain adaptive responding, potentially through cortical and striatal valuation signaling. Indeed, activity in the mediodorsal thalamus is related to the expected utility (preference governed by imagined value) of decision-making (Zhang and Hirsch, 2013), and has previously been reported when choosing the delayed reward (Sripada et al., 2011).

Finally, we detected stronger activation in high-risk youth, relative to psychiatric controls, in the left PHG during delay and control choices. The PHG has a specific role in decision-making processes as evidenced by DD-elicited activation (relative to finger tapping) (Wesley and Bickel, 2014), and is activated during expectation of a monetary reward (Ramnani and Miall, 2003). Plausibly, high-risk youth experience a stronger emotional response to an anticipated future monetary reward than psychiatric control youth. Alternatively, the group differences in both the delay and control condition may involve the PHG's role in classification, e.g., as previously shown in correctly identifying sex from multiple pictures (Han et al., 2009). Both trial types require magnitude discrimination, with control trials being simple magnitude discrimination, which could require greater PHG recruitment for high-risk participants to complete. Our results suggest that simple numerical magnitude discrimination control trials may be suboptimal as a control and are better suited to distinguish preadolescent groups. Recent work suggests that the age of our sample (11–12) is when network recruitment for magnitude discrimination begins to compare to adults (Skagenholt et al., 2021).

While our present whole-brain results yielded similar network recruitment as in heavy drinkers/AUD (Amlung et al., 2014) and healthy controls (de Water et al., 2017), the family history differences are an entirely novel finding, with no extant literature testing DD in at-risk, pre-adolescent youth (11–12 years old) and none contrasting psychiatrically matched groups without family histories of SUD. Rodriguez-Moreno et al. (2021) investigated DD neural activation in high-risk adolescent youth (15 years old) in comparison to healthy controls and found no group differences. Here we explored each choice type separately using a conventional DD task while Rodriguez-Moreno et al. examined immediacy (now vs. not-now trials and smaller sooner rewards compared to baseline) and relative reward difference (difference in dollar amounts between the smaller sooner and larger later trials) rather than delay using a novel adaptation of the conventional DD task. In line with our findings, they found no group differences in activation during the immediate choice. However, it is difficult to juxtapose our significant family history findings with their results as the effect of family history was observed in delay and control choice types, which they did not directly investigate.

Although prior work using risk-taking (BART—Hulvershorn et al., 2015), (IGT—Acheson et al., 2009) or reward-seeking (MID—Andrews et al., 2011; Bjork et al., 2008; Müller et al., 2015; Stice and Yokum, 2014) tasks have revealed FH differences in the striatum, dlPFC, OFC, anterior insula, and ACC, we did not detect differences in these regions. It is possible that family history effects in these regions are minimal during non risk-taking/reward-seeking behavior (Wilson et al., 2018), as Rodriguez-Moreno et al. (2021) also saw activation of these regions, but observed no group differences, converging with our findings. Notably, both Rodriguez-Moreno et al. and the current study observed weak engagement of the striatum during task (see Inline Supplementary Figure 5). A large body of work implicates the ventral striatum in anticipation of wins and losses using in-task notification (Wilson et al., 2018), but traditional DD tasks lack a gain notification and therefore may not robustly activate striatal systems linked to visual confirmation of rapid reinforcement.

4.1. Limitations

The present study has several limitations, including the sample size of each group. As such, we did not examine potential interactions of family history with biological sex, race/ethnicity, or socioeconomic

status. Future studies will ideally test larger samples that allow exploration of these potential interactions. Although the goal of the present work is to identify possible heritable brain biomarkers for substance use, we acknowledge that genetics, environment, and the interaction of the two contribute to adolescent substance use (Silberg et al., 2003). While we believe our participants were substance naïve, we cannot be fully confident, as assessment relied on adolescent and parental reporting, with a confirmatory urine drug screen (limited by a relatively short detection window). The requirement for an ADHD diagnosis in the high-risk and psychiatric control participants raises the possibility of long-term medication impacting brain functioning in these groups (although acute effects were prevented by a 24-hour withholding period before the scan day). Due to the novelty of fMRI delay discounting in this population, we controlled for false positives at the condition level rather than the study level and results might contain more false positives using this strategy. While we would expect steeper discounting in high-risk youth (Dougherty et al., 2014), our methods precluded precise behavioral DD measures of k or AUC with an adjusting task, due to our focus on neuroimaging outcomes and use of a non-adjusting task. Future studies should ideally collect discounting behavior both in and out of scanner—at the very least to identify correlated factors. Finally, we cannot be sure the observed differences in brain function during DD are heritable factors, as we cannot rule out the influence of learned environmental factors.

5. Conclusion

Our results show, for the first time, that a family history of SUD and externalizing disorders produce differential brain engagement during intertemporal decision-making, prior to substance use initiation compared to externalizing alone or healthy control groups. Examining brain activity during DD in high-risk youth, before drug use, permits investigations of the influence of heritable SUD risk factors on brain function during critical tasks, such as intertemporal decision-making. Prior literature largely attributed SUD risk to difficulties associated with disorders of impulsivity (for review see Verdejo-García et al., 2008). By including a psychiatric control group comprised of youth with externalizing disorders, we have identified neural activation differences, across various contrasts and regions that are unique to, or of greater magnitude, in youth with heritable risk for SUDs. These findings may indicate impairments in insula-driven time encoding and emotional discomfort with tolerating reward delay, increased thalamic involvement in task execution, and parahippocampally driven magnitude discrimination. Ongoing longitudinal follow-up data collected every six months on drug use by these participants will provide key insights to the relationships between pre-drug brain activation and later substance use—potentially revealing early-detection brain biomarkers.

6. Data availability statement

The data detailed in this paper are part of an ongoing longitudinal study and will be made public at the conclusion of the study. Until then, the data that support the findings of this study are available from the corresponding author upon reasonable request.

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CRedit authorship contribution statement

Tarah J. Butcher: Formal analysis, Visualization, Writing - original draft. **Mario Dziedzic:** Data curation, Methodology, Resources, Software, Writing - review & editing. **Jaroslav Harezlak:** Formal analysis, Writing - review & editing. **Leslie A. Hulvershorn:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing - review & editing. **Brandon G. Oberlin:** Funding acquisition, Methodology, Resources, Software, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.nicl.2021.102772>.

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