DELAY DISCOUNTING IN AT-RISK PREADOLESCENTS: BRAIN MECHANISMS AND BEHAVIOR

by

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Dedicated to my father in celebration of two and a half years of sobriety.

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ABSTRACT

It is well documented that adolescent substance use is associated with deficits in brain function and behavior. However, possible deficits that predate substance use initiation remain poorly characterized in preadolescents at-risk for developing substance use disorder (SUD). To characterize potential brain and behavioral differences that predate substance use, substance naïve preadolescents, ages 11–12, were recruited into three groups to complete functional magnetic resonance imaging delay discounting: (1) High-risk youth (*n*=35) with a family history of SUD and externalizing psychiatric disorders, (2) psychiatric controls (*n*=35) with no family history of SUD, but equivalent externalizing psychiatric disorders as high-risk youth, and (3) healthy controls (*n*=29) with no family history of SUD and minimal psychopathology. While no behavioral differences between groups were identified, there were group differences in posterior cingulate cortex (PCC) function during decision making. Specifically, the high-risk group showed stronger deactivation of the PCC than healthy controls. These results suggest that high-risk preadolescents may need to suppress activity of key nodes of the default mode network (a task negative network) to a greater extent to properly allocate attention to the task.

INTRODUCTION

Adolescent Substance Use: Overview of the Problem

Over one million adolescents (ages 12-18) in the United States meet criteria for a substance use disorder (SUD; SAMHSA, 2020). High adolescent SUD rates are particularly alarming due to critical neurodevelopment occurring during this period, with consequences including deficits in brain morphology, function, and decision-making (for review see Hamidullah et al., 2020). Though adolescent SUD remains a significant public health issue, potential brain and behavioral differences that predate substance use initiation, which could serve as markers of future substance use, remain poorly characterized. Therefore, the goal of the present study was to identify premorbid brain and behavioral differences in delay discounting (DD) in drug-naïve pre-adolescents on a spectrum of risk for developing SUD based on family history and externalizing psychopathology.

Delay Discounting: A Brief Description

While the broad construct of impulsivity has recently received criticism for lacking precision, DD is a specific behavioral tendency that measures the extent to which smaller, immediate rewards are valued over larger, delayed rewards (Ainslie, 1975). DD task performance is heritable (Anokhin et al., 2011; Oberlin & Grahame, 2009), stable over time (Kirby, 2009; Ohmura et al., 2006), longitudinally predicts SUD (Acheson et al., 2019), and tracks with family history of SUD (Dougherty et al., 2014; Rodriguez-Moreno et al., 2021). Therefore, DD is a behavioral endophenotype that could reveal causal mechanisms pertinent to both SUD and cognitive impulsivity.

Delay Discounting Behavior in At-Risk Youth

Healthy preadolescents (10-12 years old) discount at steeper rates than older adolescents and young adults (Steinberg et al., 2009), which can partially be explained by an underdeveloped ability to recognize long-term consequences of decisions during preadolescence (Grisso et al., 2003). Despite a baseline of steep discounting in this age group, preadolescent youth with a family history of SUD (Dougherty et al., 2014) or attention-deficit hyperactivity disorder

(ADHD; Costa Dias et al., 2013; Scheres et al., 2010) discount future rewards more steeply than healthy controls, and this effect persists into adolescence (Mies et al., 2019; VanderBroek et al., 2016). However, it remains unclear if these risk groups share common mechanisms for increased cognitive impulsivity, or if insensitivity to future consequence develops by divergent mechanisms.

Functional Brain Differences in At-Risk Youth

Functional magnetic resonance imaging (fMRI) during a DD task has only recently been studied in drug naïve, family history positive adolescents (Rodriguez-Moreno et al., 2021) and preadolescents (Butcher et al., 2021), with conflicting findings. Rodriguez-Moreno et al. (2021) found no differences in brain activation during a DD task between adolescents with and without a family history of SUD, while Butcher et al. (2021) found that at-risk youth, compared to controls in a preadolescent sample, showed stronger engagement of the posterior insula, parahippocampal gyrus, and thalamus when selecting the delayed choice (note: the sample from Butcher et al. (2021) overlaps with the current study sample). However, Butcher et al. only observed differences during the delayed choice while Rodriguez et al. did not examine the delayed choice alone, therefore it is difficult to juxtapose results. Both studies did, however, observe normal activation of default mode, executive control, and reinforcement/learning systems involved in the DD task, consistent with reports from healthy youth (de Water et al., 2017; Hamilton et al., 2020).

Although fMRI during a DD task has yet to be studied directly in ADHD preadolescent samples (excepting Butcher et al. (2021)), relationships with task performance and resting state connectivity have been assessed in this age group. Costa Dias et al. (2013) found that increased corticostriatal connectivity related to steeper discounting in ADHD youth. A recent meta-analysis of fMRI reward anticipation tasks (including DD) in older ADHD samples reported hyporesponsiveness of striatial structures (Plichta & Scheres, 2014). This is in line with findings from samples with disruptive behavior disorder (DBD), who also showed decreased activation of the ventral striatum (VST) during notification of reward (Cohn et al., 2015) and decreased activation of the ventromedial prefrontal cortex (vmPFC) during reward value feedback (White et al., 2013). Therefore, hyporesponsiveness, but increased synchrony of structures in the

mesocorticolimbic reward system both seem to relate to cognitive impulsivity associated with externalizing psychopathology.

Other literature in at-risk adolescents has revealed aberrant function of key nodes of the default mode and sensorimotor networks, such as the posterior cingulate cortex (PCC) and premotor cortex. ADHD adolescents showed a blunted response of the PCC during response inhibition tasks (Rubia et al., 2005), which comports with evidence that activity in this region mediates visuospatial attention (Small et al., 2003). However, other work reports that the PCC is also involved in delay gratification (Wittmann et al., 2007), but it is not clear if a blunted response of this region is also observed during DD in ADHD preadolescents. Next, increased activity of the premotor cortex correlated with decreased discounting in ADHD adolescents (Chantiluke et al., 2014), and youth with a family history of SUD showed decreased connectivity of this region to structures responsible for task execution (Vaidya et al., 2019). While aberrant function of this region has been reported in at-risk populations, it remains unclear whether the function of this region is altered in at-risk youth during decision making tasks.

Trait Urgency in At-Risk Youth

Urgency is the tendency to act rashly in response to extreme negative and positive emotional states. Negative and positive urgency are strongly correlated (Cyders et al., 2007; Zapolski et al., 2009), well documented as being predictive of and related to substance use issues in adolescence and adulthood (Cyders et al., 2014; Cyders et al., 2015; Pang et al., 2014; Robinson et al., 2014; Stautz & Cooper, 2014, 2015; Verdejo-Garcia et al., 2007; Zapolski et al., 2009), and predictive of risky behavior in preadolescence (Boyle, 2014; Zapolski et al., 2010). A recent study found that urgency and DD are related to one another and mediate the relationship between childhood adversity and later substance use (Levitt et al., 2021), and trait urgency may be related to activity of the vmPFC (Um et al., 2019), due to its role in emotion-based decision making (Bechara et al., 2000; Cyders et al., 2014; Naqvi et al., 2006). However, the relationship between neural activation in the vmPFC during decision making and trait urgency has yet to be explored in preadolescence.

Specific Aims and Hypotheses

The current behavioral and neuroimaging literature surrounding SUD risk lacks consensus, therefore, the primary goal of the present study was to investigate open-ended questions in the field.

Aim 1

Characterize brain activation for choice and control trials during the DD task.

Hypothesis 1

The orbital frontal cortex (OFC) and PCC will be recruited during choice, but not control trials, as these regions are known to encode subjective value of monetary rewards (Kable & Glimcher, 2007).

Aim 2

Investigate differences in behavior and brain activation during the DD task in preadolescents at varying risk of developing a SUD.

Hypothesis 1

Those in the high-risk and psychiatric control group will discount future rewards more steeply than those in the control group.

Hypothesis 2

A delayed reaction time effect (responding quicker to delayed trials than healthy controls) has been observed in adolescents with ADHD (Rubia et al., 2009), but has not been assessed in preadolescents. It is hypothesized that healthy controls will take longer to consider their choice options than high-risk and psychiatric control participants when selecting the delayed reward.

Hypothesis 3

During choice trials healthy controls will show stronger activation of the PCC than high-risk or psychiatric control youth.

Hypothesis 4

While it is known that older ADHD and DBD samples exhibit hyporesponsiveness of structures in the mesocorticolimbic system during reward anticipation tasks (Cohn et al., 2015; Plichta & Scheres, 2014; White et al., 2013), it remains unclear if this pattern holds in preadolescent samples. It is hypothesized that high-risk and psychiatric control youth will show decreased activity in the ventral striatum, ventral tegmental area (VTA), and vmPFC, compared to controls.

Hypothesis 5

Those in the high-risk group will shower weaker activation of the premotor cortex than those in the psychiatric and healthy control groups.

Aim 3

Investigate the relationship between Urgency, Premeditation (lack of), Perseverence (lack of), Sensation Seeking, Positive Urgency (UPPS-P) negative and positive urgency and activity in the vmPFC when the immediate reward is chosen.

Hypothesis 1

Self-reported urgency will negatively correlate with activation in the vmPFC during immediate choice across the whole sample.

METHODS

Participants

One hundred eighty six right-handed 11–12-year-old male and female preadolescents were enrolled in a 5-year longitudinal study, and 99 had usable DD task data available. 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 (APA, 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. Psychiatric control 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. Healthy control 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 (Table 1). 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; psychopharmacologic 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 midwestern medical school campus and approved by the university's Institutional Review Board.

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 2). Diagnoses were confirmed through a consensus diagnostic process with a team of clinicians. Parents also completed the Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994) to assess paternal SUD (Table 3). If the father was unavailable for screening, the non-patient edition was given to the available parent or guardian regarding the father. Maternal drug use was not exclusionary but was not sought out during recruitment to limit the probability of *in utero* drug exposure. Youth were IQ screened using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), and completed the UPPS-P-C impulsive behavior scale (Zapolski et al., 2010) that consists of five subscales: negative urgency (Cronbach's α=0.79), lack of premeditation (α=0.80), lack of perseverance (α=0.88), sensation seeking (α=0.92), and positive urgency (α=0.67).

fMRI Delay Discounting Task

Before beginning the standard 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, 3 months, 6 months, & 1 year (5 trials at each delay). 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 participant with the median discounting rate, from the initial n=21, was

presented with a randomized trial order for the remaining participants (*n*=78). Participants performed the DD task in two consecutive scans. Since out-of-scanner DD data were not collected for all participants, 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)) from the in-scanner tasks was used as a behavioral variable. 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, it was confirmed that it did not differ between the initial 21 and remaining 78 participants (0.38 ± 0.23 and 0.46 ± 0.23, respectively; independent samples *t-test* $p = 0.16$).

Image Acquisition

Imaging was performed on a Siemens 3T Prisma (Erlangen, Germany) MRI scanner using a 32-channel head coil array. During two DD scans (7:25 each) 365 whole-brain blood oxygenation level dependent (BOLD) contrast volumes were acquired using a multiband 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, 2.5×2.5×2.5 mm^3 voxels, 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=1560/49.8ms; 5 A-P and 5 P-A phase direction volumes) with the same coverage, voxel size, and slice acceleration as the BOLD acquisition. A high resolution, T1-weighted, anatomic volume (3D magnetization prepared rapid gradient echo (MP-RAGE); 5:12 min; 176 sagittal slices; 1.05×1.05×1.2 mm^3 voxels; GRAPPA R=2 acceleration) was acquired at the beginning of the imaging session.

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 *mcflirt* (Jenkinson et al., 2002), brain extraction with *bet* (Smith, 2002),

registration to participant's T1 image and MNI152 standard space, and 6mm FWHM Gaussian filter spatial smoothing. FSL's MELODIC version 3.15 automatically estimated and retained optimal number of independent components for each scan (*M*=81, SD=14.7 across all scans in the sample). Scans with a high mean absolute (> 2mm) 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* (*ANOVA*, *p*=0.21). To ensure robust processing, independent component analysis (ICA)-based data cleaning was performed, following the recommendation of Eklund et al. (2019). An unsupervised ICA-AROMA (Pruim et al., 2015) classifier was employed, 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 2mm isotropic voxels, and analyzed in FSL using voxel-level inferences that are reported to achieve a nominal false positive rate (Eklund et al., 2016). Individual-level responses to immediate and delayed choices and control trials were modeled using the canonical hemodynamic response function (HRF) in FSL. To capture the decision-making period, the HRF of each trial (mean inter-trial interval=11s; see Fig 1 for trial example) was modeled using the epoch starting 400ms after choice presentation (accounting for semantic comprehension (Hagoort et al., 2004)) and 50ms before the response (to minimize motor signal (Pfefferbaum et al., 1985)). A high-pass filter set to (1/90 Hz) was used to remove low-frequency noise.

Statistical Analyses

Statistical analyses were conducted in SPSS (IBM; v26) or FSL. All statistical assumptions were either met or corrected for. Specific methods of analysis are described in the results.

RESULTS

Aim 1: Choice and Control Trial Brain Activation

The goal of aim 1 was to characterize brain activation for choice and control trials across all participants. Under this aim, [Choice>Control] and [Control>Choice] contrasts from individual level models for each participant were entered into two separate general linear models (GLM) in FSL (FMRIB's Local Analysis of Mixed Effects (FLAME) stage 1) one-sample *t*-tests (voxel-level significance, corrected for whole-brain family-wise error (FWE), $p_{FWE} < 0.05$, cluster threshold = 10). Choice trials, compared to control trials, elicited stronger activation of the OFC, PCC, and hippocampal regions (Fig 2A, B). Control trials, compared to choice trials, elicited stronger activation of temporal gyrus, supramarginal gyrus, and inferior frontal regions (Fig 2C). For a full list of activated regions in the [Choice>Control] and [Control>Choice] contrasts see Table 4.

Aim 2: Delay Discounting Behavior and Brain Responses in At-risk Preadolescents

The first goal of aim 2 analyses was to determine if differences in DD behavior were present between groups. To analyze in scanner behavioral differences, an immediate choice ratio (see fMRI DD task paragraph for more details) was calculated. One-way ANOVA of the immediate choice ratio showed no behavioral differences between groups during task, [$F(2, 96) = 1.90$, $p = 0.16$; Fig 3A]. An additional one-way ANOVA was conducted on out of scanner DD behavior in a subset of subjects with adjusting task data (n=45). Fitted parameter k was log transformed to normalize the data before analysis, and did not differ between groups, [$F(2, 42) = 1.12$, $p = 0.34$; Fig 3B]. Next, the delayed choice reaction time (RT) effect (mean immediate trial RT – mean delayed trail RT (Rubia et al., 2009)) was calculated for each participant and tested for group differences using a mixed ANOVA with scan as a within subjects factor, and group as a between subjects factor. There was a main effect of scan, [$F(1, 96) = 4.10$, $p < 0.05$; Fig 4], such that participants took longer to respond to immediate trials during the first scan ($m = -0.12$) but longer to respond to delayed trials during the second scan ($m = 0.08$). There were no differences in the delayed reaction time effect between groups, [$F(2, 96) = 0.54$, $p = 0.58$; Fig 4].

The second goal of aim 2 analyses was to determine if differences in brain responses during the DD task were present between groups. It was hypothesized that those in the healthy control group would show stronger activation of the PCC and premotor cortex than the high-risk group during choice, compared to control trials. To test these hypotheses, [Choice>Control] contrasts from individual level models for each participant were entered into a GLM FLAME1 inter-group *F*-test in FSL. Furthermore, it was hypothesized that those in the high-risk and psychiatric control groups would show weaker activation of structures in the mesocorticolimbic system, specifically the vmPFC, VST, and VTA. To test this hypothesis, [Immediate>Control] contrasts were also entered into an inter-group *F*-test in FSL. Group differences were inferred using voxel-level significance at $p_{FWE} < 0.05$, cluster threshold = 10. No areas of activation survived in the whole-brain analyses after correction for multiple comparisons. Subsequent analyses were conducted to test for group differences within the regions of interest defined by the hypotheses (ROIs; Fig 5).

Mean parameter estimates were extracted from each ROI (see Fig 5) with FSL's featquery (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT/UserGuide) using Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006), except for the VTA, for which the Automated Anatomical Labelling Atlas 3 (AAL-3; Rolls et al., 2020) was used. ANOVA was used to test for differences in activation in the PCC and premotor cortex, and MANOVA was used to test for differences in the structures of the mesocorticolimbic system. MANOVA was used to test for mesocorticolimbic system differences to examine differences in each structure (VTA, VST, and vmPFC) while also controlling for correlation between dependent variables. Sex was used as a covariate in all three analyses. There were significant group differences in activation of the PCC [$F(2, 95) = 3.72$, $p < 0.05$; Fig 5A], and Bonferroni pairwise comparisons revealed the high-risk group ($m = 25.57$) showed stronger activation than the healthy control group ($m = -0.15$; $p < 0.05$), which was opposite of the hypothesis. Since the [Choice>Control] contrast involves double subtraction (i.e. Choice–Baseline>Control–Baseline), it is possible that the effects observed are actually due a difference in deactivation, rather than a difference in activation. To clarify the observed differences, parameter estimates were extracted from the [Choice>Baseline] and [Control>Baseline] contrasts and tested for group differences. Differences in the [Choice>Control] contrast were driven by differences in deactivation in the [Choice>Baseline] contrast, [$F(2, 95) = 4.36$, $p < 0.05$; Fig 5B,

C], such that the high-risk group ($m = -25.11$) showed stronger deactivation to choice than the control group ($m = -6.40$; $p < 0.05$). There was a trend toward group differences in the premotor cortex, [$F(2, 95) = 2.45$, $p = 0.09$; Fig 6], and no group differences were observed in the structures of the mesocorticolimbic system, [$F(8,184) = 0.85$, $p = 0.57$; Wilk's Λ=0.93; Fig 7].

Aim 3: Activation During Immediate Choice Shows No Relationship with Self-report Urgency

The goal of aim 3 was to examine the relationship between brain activation during immediate choice and the UPPS-P negative and positive urgency subscales. Since the two subscales are often strongly correlated (Cyders et al., 2007; Zapolski et al., 2009), an average urgency score was calculated for each participant by taking an average of the positive and negative subscales. Urgency was used as predictor in a GLM FLAME1 linear regression in FSL with the [Immediate>Control] contrasts from each participant as the dependent variable (voxel-level significance, $p_{FWE} < 0.05$, cluster threshold = 10). It was hypothesized that urgency would negatively correlate with activation in the vmPFC, but no areas of activation survived the whole-brain analysis after correction for multiple comparisons. Additional analyses were conducted to test for a relationship specifically within the vmPFC ROI. Mean regression parameter estimates from the [Immediate>Control] contrast were extracted from the vmPFC and were tested for correlation with urgency, [$r(97) = 0.05$, $p = 0.66$]. Activation values from the vmPFC were also tested for correlation with negative urgency alone, [$r(97) = -0.04$, $p = 0.72$], as positive urgency had questionable internal reliability (Cronbach's $\alpha = 0.67$).

DISCUSSION

The goal of the present study was to investigate brain and behavior differences prior to drug exposure using a DD task in preadolescents at varying risk for SUD based on family history and externalizing psychopathology. No behavioral differences were observed, and the PCC was the only brain region that displayed group differences in activation during the task. Results from Aim 1, investigating brain activation during choice and control trials across the whole sample, indicated normal activation patterns of posterior default mode, executive control, and learning/reinforcement networks (Fig 2; Table 4) across all participants. The hypothesis that the OFC and PCC would be active during choice, but not control trials was supported. Activation patterns in the present sample reflected that of healthy youth (de Water et al., 2017; Hamilton et al., 2020) and adults (for review see Frost & McNaughton, 2017).

Results from Aim 2 investigating differences in DD behavior and brain activation between groups indicated no behavioral differences and few brain differences. The hypothesis that high-risk and psychiatric control youth would discount future rewards at steeper rates than healthy control youth was not supported. This contradicts previous reports that preadolescents with a family history of SUD (Dougherty et al., 2014) and ADHD (Costa Dias et al., 2013; Scheres et al., 2010) show steeper discounting on the DD task. Multiple factors may have contributed to the lack of behavioral differences observed in this sample. First, sample sizes are small (~30 in each group) and may have left us underpowered to detect an effect. Second, each participant only completed 30 choice trials in both the adjusting and in the scanner tasks (note the in scanner task was completed twice for a total of 60 trials). The small number of trials completed per participant also may have contributed to being underpowered to detect an effect. Previous studies reporting behavioral differences in the age group included larger samples and/or more trials (Costa Dias et al., 2013; Dougherty et al., 2014; Scheres et al., 2010). Third, a floor effect was observed: All three groups discounted future rewards at steep rates (Fig 3), comporting with previous findings that preadolescents are already impulsive regardless of risk status (Steinberg et al., 2009), which is likely explained by the underdeveloped ability to understand future consequences of present choices at this age (Grisso et al., 2003).

The second hypothesis of Aim 2 was not supported. It was expected that healthy controls would take longer to consider their choices than high-risk and psychiatric controls when

selecting the delayed reward. This effect had been previously observed in a sample of ADHD adolescents (Rubia et al., 2009) but could not be replicated in the present preadolescent sample (Fig 4). Time perspective and orientation has long been noted as a developmental marker of adolescence (Lewin, 1939; Piaget, 1955). For example, participants took longer to respond to immediate, compared to delayed, choice trials in the first scan. It is possible future orientation may have been difficult for the entire sample due to developmental stage, leading to short deliberation times when the future reward was selected.

The third hypothesis of Aim 2 was that those in the control group would show stronger engagement of the PCC during choice trials than the high-risk and healthy control groups, but the opposite effect was observed: High-risk youth showed stronger activation of the PCC than healthy control youth (Fig 5A, B). Previous work reports less engagement of this region during inhibitory tasks in ADHD samples (Rubia et al., 2005). Authors posit that this deficit is due to a reduced capacity in ADHD persons to allocate attention, and that this may be generalizable other executive tasks as PCC activation during a risk taking task in adults correlated with ADHD symptom severity (Ernst et al., 2003). While response inhibition, risk taking, and decision making tasks all loosely fall under the umbrella of impulsivity, they are separate constructs (Strickland & Johnson, 2020). The present study provides evidence that blunted PCC activity in ADHD patients is not generalizable across multiple task domains.

Differences in the opposite direction than hypothesized in the PCC are also counterintuitive to previous reports that ADHD patients have difficulty regulating default mode network (DMN) activity in order to respond to external demands during task, leading to attenuated deactivation (Helps et al., 2010; Liddle et al., 2011). The PCC finding in the present study was driven by deactivation differences during choice compared to baseline activity, and strength of deactivation was high-risk > psychiatric control > healthy control (note that the difference between psychiatric and healthy controls was not significant; Fig 6B). One study showed that as task difficulty increased, ADHD participants showed stronger, albeit not significant, deactivation of the PCC (Fassbender et al., 2009). It is possible that more simple tasks could lead to less engagement of the PCC and more cognitively demanding tasks could lead to stronger disengagement of nodes of the DMN in order to keep necessary attention on the task. Another study found that aberrant DMN suppression in ADHD was dependent on interstimulus interval (ISI) length (Metin et al., 2015). In tasks with short (1-4s) and long (7-10s)

ISIs ADHD participants showed less suppression of the DMN than controls. However, with medium (3-6s) ISIs, ADHD DMN suppression patterns were not different from controls. Authors interpreted these findings to mean that DMN suppression may only fail in ADHD persons when energy expenditure for keeping the DMN suppressed during task is suboptimal. The present study had a mean ISI of 4.25s (Fig 1), which falls into the optimal energy expenditure range defined by Metin et al. (2015)'s findings. Psychiatric control youth did not differ from controls in DMN suppression, however, high-risk youth did, suggesting family history of SUD may require additional suppression of DMN activity to keep focus during task.

The fourth hypothesis of Aim 2 was that high-risk and psychiatric control youth would show decreased activity in the VST, VTA, and vmPFC in comparison to controls. This hypothesis was not supported as there were no differences in activity between groups in these regions (Fig 6). These findings are contrary to previous meta-analyses showing hyporesponsivness of the VST and vmPFC during decision making and reward tasks (Alegria et al., 2016; Plichta & Scheres, 2014), and the vmPFC during reward feedback (White et al., 2013), in those with externalizing psychopathology. Previous literature in those with a family history of SUD is less clear about activity in these regions as the current findings are consistent with some studies (Bjork et al., 2008; Muller et al., 2015; Yarosh et al., 2014), but contradictory to others (Andrews et al., 2011; Hulvershorn et al., 2015). It is important to note that the aforementioned studies mainly included tasks that would be classified under the risk sensitivity domain, rather than the delayed consequence sensitivity domain where DD falls (Strickland & Johnson, 2020). Risk sensitivity tasks typically include in-task notifications of wins and losses, which are reported to robustly activate mesocorticolimbic structures involved in reward (Wilson et al., 2018). Traditional DD tasks lack in task notifications of gain, and therefore may not consistently activate mesocorticolimbic structures. Indeed, Zhang and Hirsch (2013) parsed apart activity related to the valuation of a reward, the temporal decay of reward, and the receipt reward, and found that striatal activity only corresponded with receipt of reward.

The fifth hypothesis of Aim 2 was that those in the high-risk group would show weaker activation of the premotor cortex than those in the psychiatric and healthy control groups. There was a trend toward group differences (p=0.09), albeit in the opposite direction than hypothesized. Deactivation in the high-risk and psychiatric control groups was similar, while the healthy control group showed stronger deactivation of this region (Fig 7). ADHD medication has shown

to upregulate activity in the premotor cortex of ADHD youth during DD (Carlisi et al., 2016), and while medication was withheld 24 hours before the scan in the high risk and psychiatric control groups, it is possible there was a lasting effect of medication leading to increased activity of these regions.

Aim 3 investigated the relationship between activation during the immediate choice in the vmPFC and UPPS self-reported urgency across the whole sample. Results indicated no relationship between the two variables, contrary to the hypothesis that a negative relationship would be observed. Previous work in adults reports that vmPFC activation during tasks with an emotional component is related to urgency (Cyders et al., 2014; Cyders et al., 2015), which comports with the theory that the vmPFC is involved in emotion-based decision making (Bechara et al., 2000; Cyders et al., 2014; Naqvi et al., 2006). The present DD task lacks a strong emotional component, especially since the age of the present sample (11-12 years old) is the first age at which money begins to be perceived as an essential economic function (Gasiorowska et al., 2012). Therefore, since the understanding that money is necessary for an exchange of goods and services is just beginning to develop, the choice between smaller sooner or larger delayed amounts of money may not involve an emotional component which could explain the lack of relationship between vmPFC activation and urgency.

Results from the present study should be interpreted within the framework of its limitations. First, determining substance naivety of the sample relied on self-report from the parent and child and a urine screen with a relatively short detection window. Second, inclusion criteria for the high-risk and psychiatric control groups included an ADHD diagnosis. This raises the possibility of long-term medication exposure impacting brain function, although acute effects were controlled for by withholding medication for at least 24 hours before the scan day. Third, the sample size was relatively small and precluded the exploration of sociodemographic variables such as biological sex, race/ethnicity, and socioeconomic status as factors in analyses. Future studies would benefit from larger sample sizes allowing the exploration of possible interactions of risk factors with sociodemographic variables. Fourth, the current methodology prevented the calculation of a precise measure of DD behavior (k) for each participant due to the use of a non-adjusting task because of a focus on neuroimaging outcomes. Future studies should collect behavioral data from both adjusting and non-adjusting tasks to identify correlated factors and better explore behavioral differences between groups.

To summarize, the different risk groups in the present study were not distinguishable by behavior on the DD task, however, activity in the PCC during choice trials did distinguish groups (for more brain differences between group see Butcher et al., 2021). The use of a preadolescent, substance naïve sample allows for the possibility that differences in PCC function between the high-risk and healthy controls groups may be a heritable risk factor for later SUD. While there were no significant differences overserved between the psychiatric and healthy control or high-risk groups, patterns of deactivation (high-risk > psychiatric control > healthy control; Fig 5) are suggestive of an additive marker of risk. Follow-up analyses with longitudinal data measuring substance use and other risky behaviors in the present sample will reveal whether differences in PCC function could serve as a predictor of these behaviors.

TABLES

Table 1. Participant Characteristics.

W – White; M – Mixed Race; AA – African American; HL – Hispanic or Latino; NHL – not Hispanic or Latino. Means are ± SD. [a]IQ data missing for 1 and 2 participants, respectively. [b]Socioeconomic 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. Continuous variables were tested for group differences using analysis of variance and categorical variables were tested for group differences using chi-square test.

	High-Risk (n = 35)	**Psychiatric Controls (n = 35)**	**Healthy Controls (n = 29)**	***p* value**
Age	11.9 ± 0.5	11.9 ± 0.6	12.0 ± 0.7	p=0.64
Male (%)	68.6	74.0	72.4	p=0.87
Race	15 W; 6 M; 13 AA	21 W; 7 M; 7 AA	14 W; 4 M; 11 AA	p=0.46
Ethnicity	1HL; 34 NHL	35 NHL	29 NHL	
IQ[a]	107.1 ± 15.6	108.3 ± 16.7	109.8 ± 12.6	p=0.78
SES[a,b]	4.7 ± 1.6	4.1 ± 1.5	4.3 ± 1.4	p=0.21
Negative Urgency	2.4 ± 0.7	2.6 ± 0.7	2.0 ± 0.6	p<0.01*
Positive Urgency	2.4 ± 0.7	2.6 ± 0.7	1.9 ± 0.7	p<0.01*

Table 2. Participant Psychiatric Diagnoses.

DSM-V – Diagnostic Statistical Manual Fifth Edition; 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. HR – high-risk; PC – psychiatric control; HC – healthy control.

DSM-V Diagnoses

	Current Disorders			**Past Disorders**		
	HR (n=35)	**PC (n=35)**	**HC (n=29)**	**HR (n=35)**	**PC (n=35)**	**HC (n=29)**
ADHD	35 (100%)	35 (100%)	0	35 (100%)	35 (100%)	0
CD	2 (6%)	2 (6%)	0	2 (6%)	2 (6%)	0
ODD	27 (77%)	22 (63%)	0	27 (77%)	22 (63%)	0
DBD	5 (14%)	11 (31%)	0	5 (14%)	11 (31%)	0
Anxiety Disorders	16 (45%)	11 (31%)	2 (7%)	17 (49%)	11 (31%)	2 (7%)
Mood Disorders	0	2 (6%)	0	3 (9%)	5 (14%)	0
Other	6 (17%)	6 (17%)	0	15 (43%)	9 (26%)	2 (7%)

Table 3. Paternal Substance Use Disorders.

Details of the paternal substance use disorder diagnoses for the high-risk group (*n*=35) from the Semi-Structured Assessment for the Genetics of Alcoholism.

High-risk Paternal DSM-5 Substance Use Disorder (SUD) Diagnoses			
	Mild	**Moderate**	**Severe**
Alcohol	5	7	17
Cannabis	12	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		

Table 4. Significant Activation for [Choice>Control] Contrast.

Peak voxel-level significance, family-wise error corrected for whole-brain multiple comparisons (p_{FWE} < 0.05, *cluster size* > 10). Secondary peaks are indented. *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. R – right; L – left; P – posterior.

Brain regions by contrast	**Cluster size**	**Peak voxel**	**Peak voxel**	**MNI**	**Coordinates**	**(mm)**
	k	p_{FWE}	***Z***	***x***	***y***	***z***
[Choice > Control]						
Visual cortex	2735	< 0.001	10.4	−16	−92	−4
		< 0.001	6.59	−2	−78	−8
		< 0.001	6.54	−36	−86	−10
		< 0.001	5.73	−36	−96	−2
Visual cortex	2057	< 0.001	9	22	−102	6
		< 0.001	8.45	20	−90	−6
		< 0.001	6.59	40	−82	−14
		< 0.001	6.46	44	−78	−6
		< 0.001	6.27	38	−82	−8
R Retrosplenial	509	< 0.001	7.34	8	−44	8
R Thalamus		< 0.001	7.26	22	−32	−2
P Cingulate		< 0.001	6.46	2	−34	40
R Hippocampus		0.001	5.29	28	−24	−14
R Middle Frontal	348	< 0.001	6.94	46	40	18
		< 0.001	6.87	42	36	18
		< 0.001	5.69	42	48	6
		< 0.001	5.68	46	34	26
		< 0.001	5.64	42	50	2
R Angular Gyrus	347	< 0.001	6.67	34	−60	34
		< 0.001	6.27	36	−66	38

Table 4, continued

		< 0.001	5.7	28	−66	46
		< 0.001	5.34	30	−72	54
		0.001	5.28	42	−76	44
Retrosplenial		< 0.001	6.47	−6	−52	12
		< 0.001	6.46	−8	−48	8
L Precuneus		< 0.01	5.12	−12	−62	24
L Paracingulate	159	< 0.001	6.2	−6	34	34
		< 0.001	6.11	−2	28	40
		< 0.001	5.78	8	30	38
		< 0.001	5.6	10	32	34
R Superior Frontal	122	< 0.001	6.36	22	44	42
L Angular Gyrus	111	< 0.001	6.41	−28	−64	38
R Superior Frontal	94	< 0.001	6.25	24	20	52
		< 0.001	6.09	28	16	54
R Orbitofrontal	66	< 0.001	5.85	22	38	−16
L Hippocampus	64	< 0.001	6.2	−22	−30	−6
Cerebellum	49	< 0.001	6.16	−40	−64	−44
R Angular Gyrus	38	< 0.01	5.25	46	−58	46
		< 0.01	5.18	42	−60	48
L Orbitofrontal	22	< 0.001	6	−20	26	−18
L Orbitofrontal	19	< 0.001	6.02	−20	40	−16
R Angular Gyrus	15	< 0.001	5.39	42	−50	46
[Control > Choice]						
R Angular Gyrus	1927	< 0.001	8.53	58	−46	24
R Temporal Gyrus		< 0.001	7.61	54	−22	−8
		< 0.001	7.19	54	−44	32
R Occipital Cortex		< 0.001	6.31	44	−62	8
R Temporal Gyrus		< 0.001	5.95	58	−44	6
R Temporal Gyrus		< 0.001	5.59	62	−34	0
Visual Cortex	1577	< 0.001	8.64	6	−88	22

Table 4, continued

		< 0.001	8.58	2	−88	20
		< 0.001	5.69	22	−86	34
L Supramarginal	1394	< 0.001	8.61	−58	−50	36
		< 0.001	6.81	−58	−42	42
L Temporal Gyrus		< 0.001	6.52	−56	−60	2
		< 0.001	6.51	−64	−36	36
L Occipital		< 0.001	6.4	−44	−72	2
L Occipital		< 0.001	6.31	−46	−64	14
L Precuneus	131	< 0.001	5.92	−8	−54	58
R Superior Parietal		< 0.01	5.25	−16	−58	56
		< 0.01	5.05	−12	−42	46
L Occipital Cortex		< 0.01	4.96	−12	−64	56
		< 0.01	4.96	−10	−48	50
R Inferior Frontal	128	< 0.001	5.89	56	34	−2
		< 0.001	5.82	48	32	−2
L Posterior Cingulate	44	< 0.001	5.89	−6	−24	42
		< 0.01	5	−10	−32	42
R Posterior Cingulate	43	< 0.001	5.71	14	−30	40
		< 0.001	5.41	6	−20	42
Precentral Gyrus	40	< 0.001	5.49	−26	−6	54
Frontal Pole	15	< 0.001	5.39	−36	42	36
Superior Frontal	13	< 0.01	5.15	−16	0	70
		< 0.01	5.02	−22	4	66

FIGURES

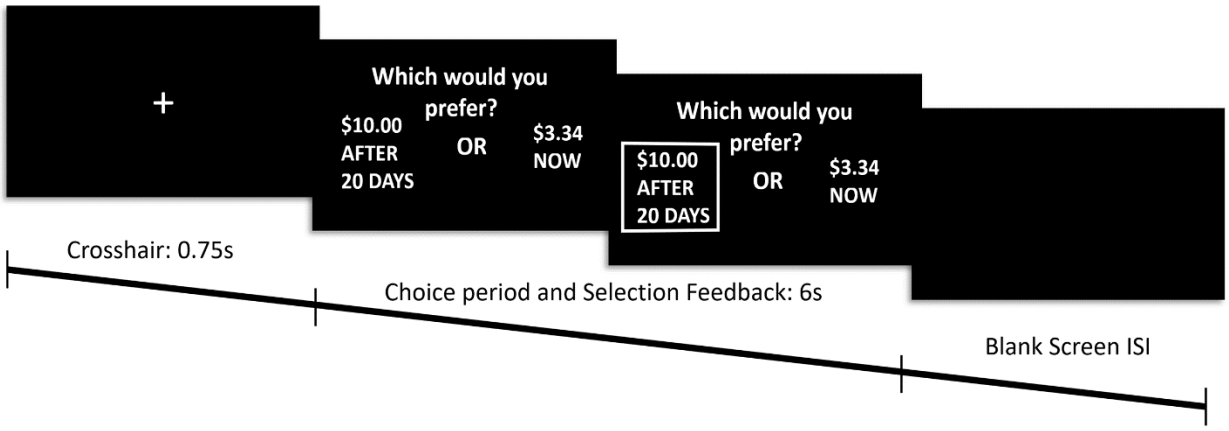

Figure 1. Schematic of a Single Choice Trial Presented During the fMRI DD Task.

Mean intertrial interval is 11 seconds. Crosshair indicates the beginning of each trial, at which point the participant has up to 6 seconds to make a choice, followed by feedback indication for up to 1 second. Blank screen mean ISI = 4.25 seconds, with 1 second jitter. ISI = interstimulus interval.

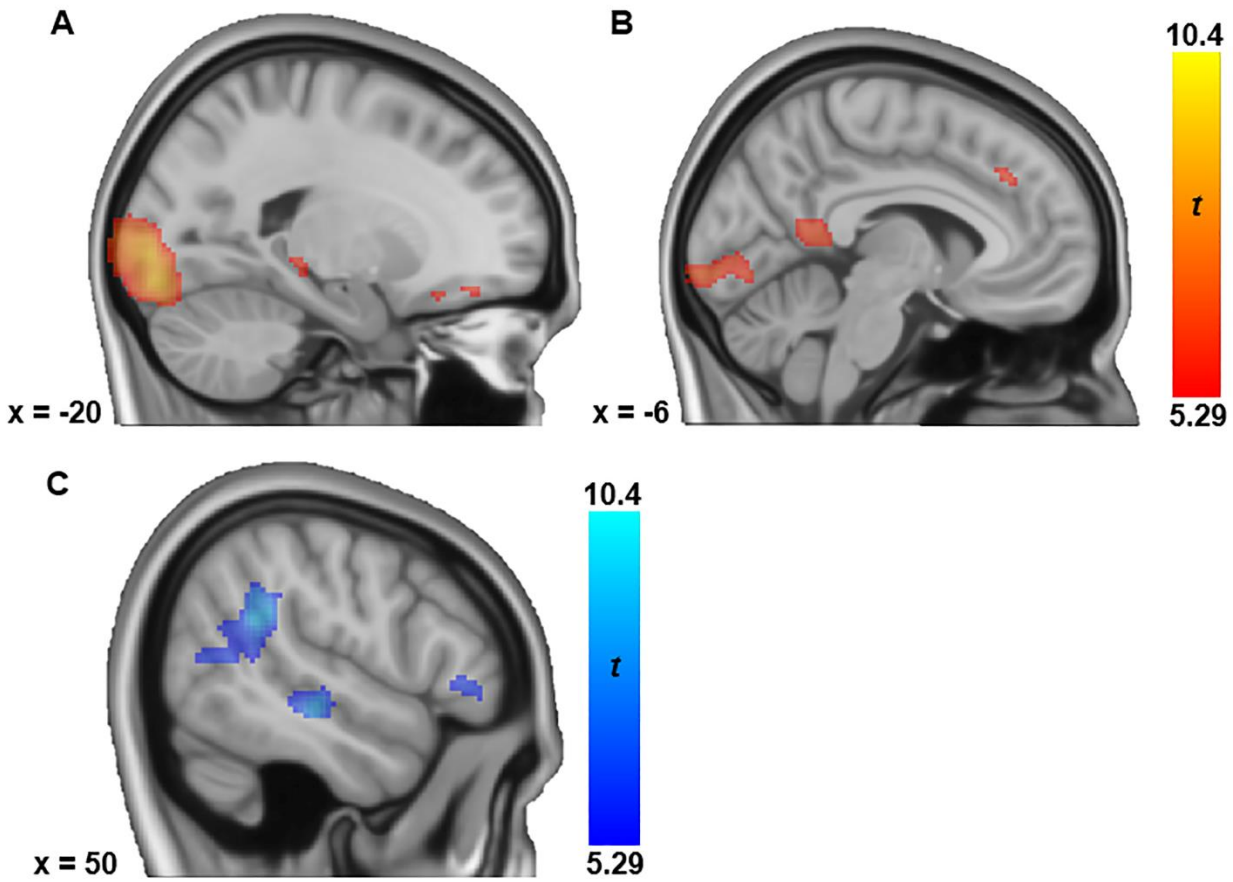

Figure 2. [Choice>Control] and [Control>Choice] Regions of Activation.

A & B: Significant clusters from the [Choice>Control] contrast included the OFC, hippocampal regions (A), and PCC (B). C: Significant clusters from the [Control>Choice] contrast included the temporal gyrus, supramarginal gyrus, and inferior frontal regions. All foci of activation meet family wise error (FWE) corrected voxel level significance, $p_{FWE}<0.05$, cluster threshold=10. For a full list of regions see Table 4.

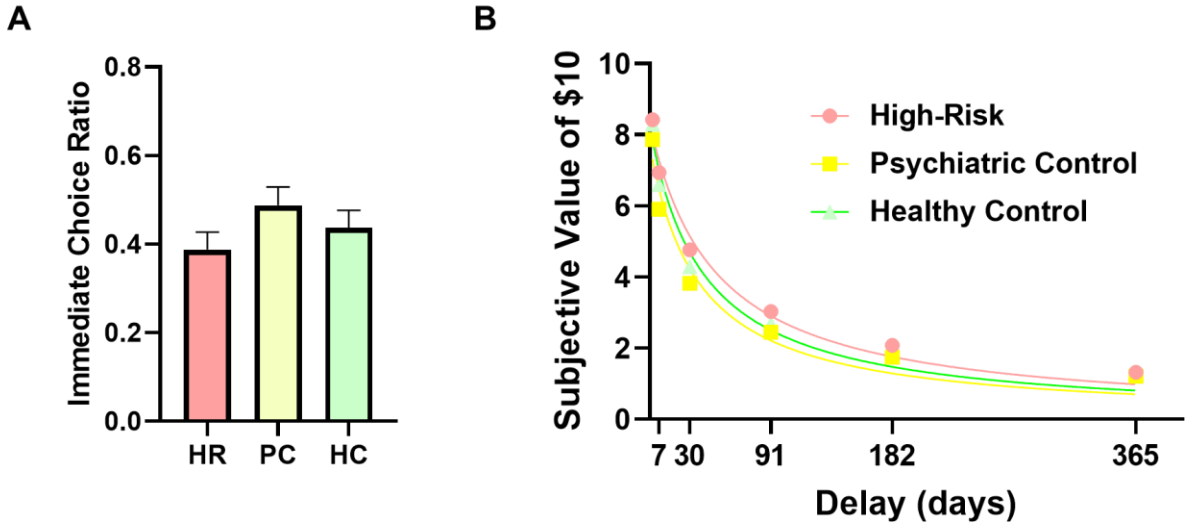

Figure 3. Behavioral Measures of Delay Discounting Show No Differences Between Groups.

A: There were no differences between groups for in-scanner behavior, as indexed by immediate choice ratio (immediate choices/total choices, excepting omissions; p=0.16). Data are displayed as mean with standard deviation. HR – high-risk; PC – psychiatric control; HC – healthy control. B: There were no differences between groups for out of scanner behavior, as indexed by k (p=0.34). Note k values were only available for a subset of participants (n=45).

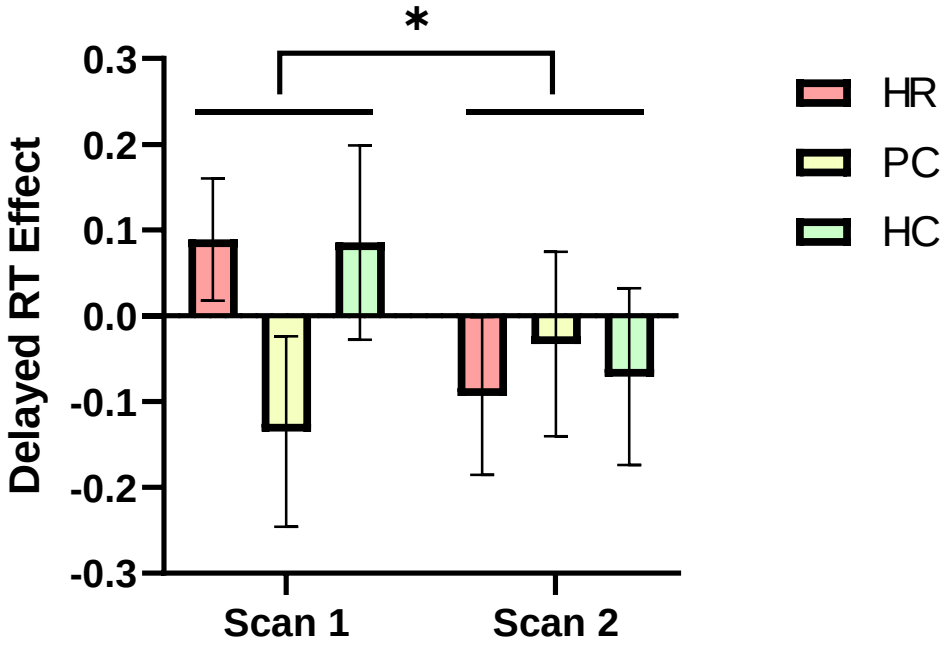

Figure 4. Delayed Choice Effect Does Not Differ Between Groups.

Groups showed no differences in the delayed reaction time (RT) effect (mean immediate trial RT – mean delayed trial RT (Rubia et al., 2009); p=0.58). There was a main effect of scan [$F(1, 96)=4.10$, $p<0.05$], such that participants took more time to respond to immediate trials in the first scan, but more time to respond to delayed trials in the second scan. Data are displayed as mean with standard deviation. HR – high-risk; PC – psychiatric control; HC – healthy control.

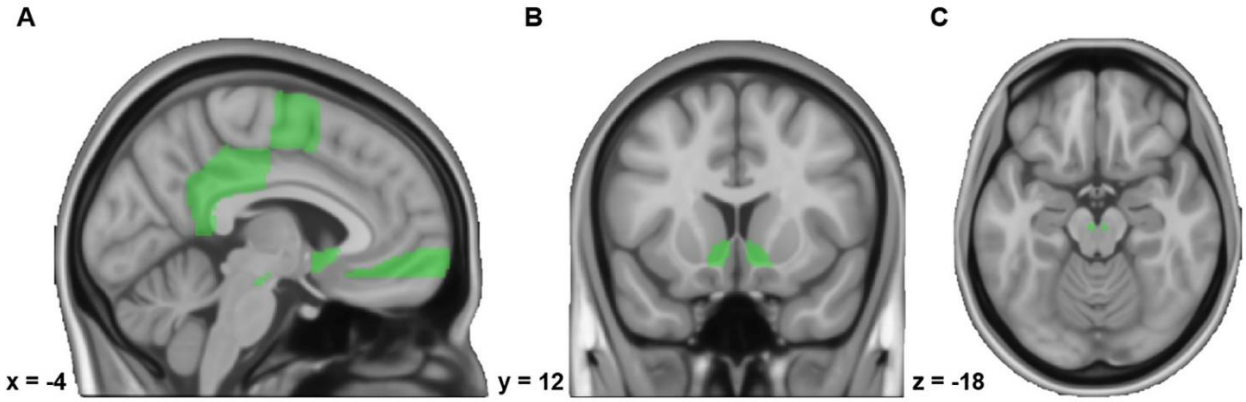

Figure 5. Regions of Interest.

A & B: Anatomical regions of interest (ROIs) from the Harvard Oxford Cortical and Subcortical atlases (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). ROIs include the posterior cingulate cortex, premotor cortex, ventromedial prefrontal cortex (A), and the ventral striatum (B). C: Ventral Tegmental Area ROI from the Automated Anatomical Labeling Atlas 3 (AAL-3; Rolls et al., 2020). Brains are displayed in neurological orientation and coordinates correspond to Montreal Neurological Institute space.

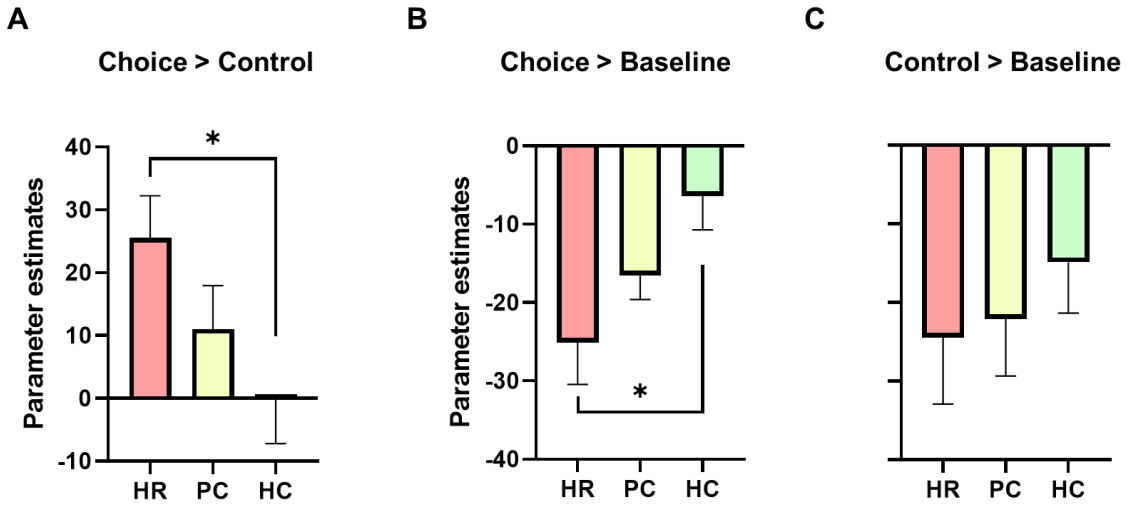

Figure 6. Activation Differences in the Posterior Cingulate Cortex.

A: There were significant group differences in activation of the PCC [$F(2, 95)=3.72$, $p<0.05$] in the [Choice>Control] contrast, and Bonferroni pairwise comparisons revealed the high-risk (HR) group ($m=25.57$) showed stronger activation than the healthy control (HC) group ($M=-0.15$; $p<0.05$). Follow-up analyses revealed that differences in the [Choice>Control] contrast were driven by differences in deactivation in the [Choice>Baseline] contrast, [$F(2, 95)=4.36$, $p<0.05$], such that the high-risk group ($m=-25.11$) showed stronger deactivation to choice than the control group ($M=-6.40$; $p<0.05$). Data are displayed as mean with standard deviation. PC – Psychiatric Controls.

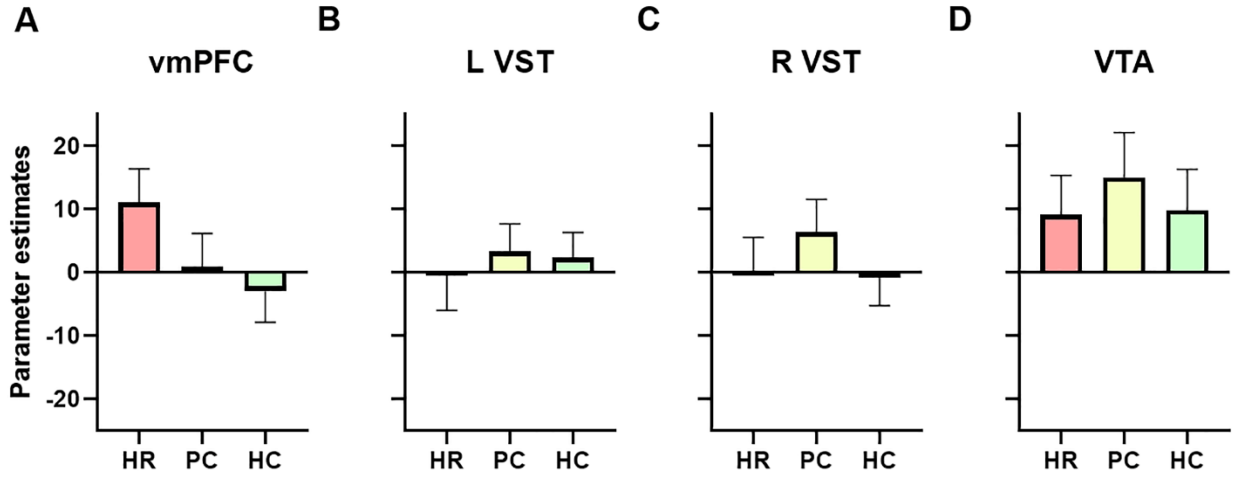

Figure 7. No Mesocorticolimbic Reward System Activation Differences Between Groups.

A, B, C, and D: There were no group differences in activation for the [Immediate>Control] contrast in the ventromedial prefrontal cortex (vmPFC) (A), left ventral striatum (L VST) (B), right ventral striatum (R VST) (C), and ventral tegmental area (VTA) (D) (p=0.57). Data are displayed as mean with standard deviation. HR – high-risk; PC – psychiatric control; HC – healthy control.

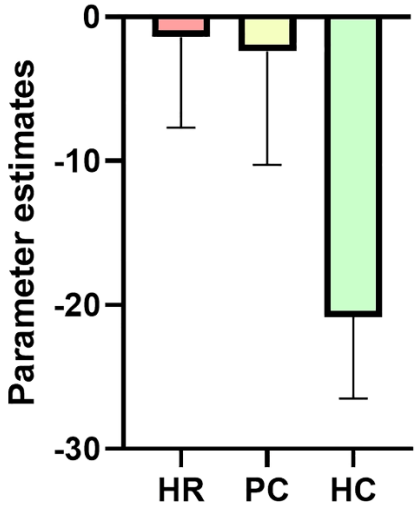

Figure 8. Trend Level Differences in the Premotor Cortex.

There were trend level differences in activation between groups in the premotor cortex in the [Choice>Control] contrast (*p*=0.09). Data are displayed as mean with standard deviation. HR – high-risk; PC – psychiatric control; HC – healthy control.

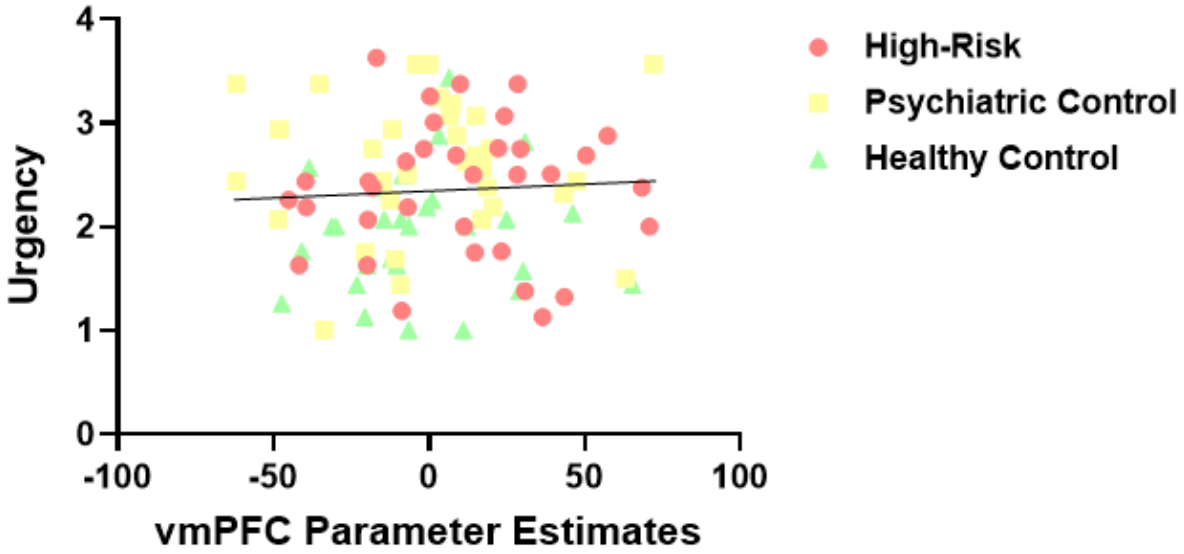

Figure 9. Urgency Does Not Predict Activation in the Ventromedial Prefrontal Cortex.

Self-reported urgency from the UPPS-P-C showed no relationship with activity in the ventromedial prefrontal cortex (vmPFC) in the [Immediate>Control] contrast [$r(97) = 0.05$, $p=0.66$].

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