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Cortical Activation Deficits During Facial Emotion Processing in Youth at High Risk for the Development of Substance Use Disorders*

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Abstract

Background—Recent longitudinal studies demonstrate that addiction risk may be influenced by a cognitive, affective and behavioral phenotype that emerges during childhood. Relatively little research has focused on the affective or emotional risk components of this high-risk phenotype, including the relevant neurobiology.

Methods—Non-substance abusing youth (N = 19; mean age = 12.2) with externalizing psychopathology and paternal history of a substance use disorder and demographically matched healthy comparisons (N=18; mean age = 11.9) were tested on a facial emotion matching task during functional MRI. This task involved matching faces by emotions (angry, anxious) or matching shape orientation.

Results—High-risk youth exhibited increased medial prefrontal, precuneus and occipital cortex activation compared to the healthy comparison group during the face matching condition, relative to the control shape condition. The occipital activation correlated positively with parent-rated emotion regulation impairments in the high-risk group.

Conclusions—These findings suggest a preexisting abnormality in cortical activation in response to facial emotion matching in youth at high risk for the development of problem drug or

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Author Disclosures

Conflict of Interest

All authors declare that there are no conflicts of interest.

Contributors

Authors L. Hulvershorn, P. Finn and A. Anand designed the study. L. Hulvershorn wrote the protocol, secured necessary regulatory approval and supervised all stages of the study. E. Leibenluft, A. Anand and P. Finn advised on subject assessment, neuroimaging acquisition and analysis. T. Hummer undertook the imaging analysis and created figures. L. Hulvershorn wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

alcohol use. These cortical deficits may underlie impaired affective processing and regulation, which in turn may contribute to escalating drug use in adolescence.

Keywords

addiction risk; child and adolescent; ADHD; externalizing; neuroimaging; prefrontal cortex

1. INTRODUCTION

1.1 Childhood Risk for the Development of Substance Use Disorders

A prominent theory for the development of substance use disorders (SUDs) suggests a latent childhood central dysregulatory trait, involving “delayed or deficient development of behavioral, emotional, and cognitive regulation” (Lejuez et al., 2010; Zucker, 2008) that interacts with environmental risk or protective factors throughout development. This liability trait or phenotype has been broadly identified as “difficult temperament” in infancy and early childhood (Lerner and Vicary, 1984; Windle, 1991) and “behavioral undercontrol” (Lerner and Vicary, 1984) and “neurobehavioral disinhibition” (Tarter et al., 2003) in childhood and adolescence. These models implicate a core disorder in self-regulation characterized by disinhibition across behavioral, cognitive and affective dimensions (Tarter et al., 1989). Longitudinal studies verify that latent childhood liability traits are stable and predict later SUDs (Dubow et al., 2008; Hayatbakhsh et al., 2009; Hill et al., 2009; Martel et al., 2009; Molina et al., 2007; Newcomb et al., 1986; Sourander et al., 2007).

1.2 Affective Risk Factors for the Development of Addictive Disorders

Despite growing interest in associations among various liability domains in childhood and SUD development, little research investigates childhood mood- or emotion-related factors, instead focusing on cognitive or behavioral risk factors (Cservenka et al., 2012; Cservenka and Nagel, 2012; Lahat et al., 2012; Molina et al., 2009; O’Connor et al., 2012; White et al., 2012). Affective research has been hampered by non-standardized terminology, overlapping models and a paucity of assessment methods. In addition, normative development of emotion regulation is an understudied, complex, and variable process, making deviation from typical development difficult to discern.

Impairments in emotional functioning have been implicated in the etiology of SUDs (Blackson, 1994; Furukawa et al., 1998; Knight et al., 1998). The “neurobehavioral disinhibition” latent trait appears to be partly composed of affectively relevant constructs, such as irritability (Tarter et al., 1995), “difficult affective or emotional temperament” (Blackson, 1994) and behavioral self-regulation (Dawes et al., 1997), along with a range of peer, parental and societal mediators that interact with emotional functioning (Feske et al., 2008; Kirisci et al., 2009; Ridenour et al., 2009).

Given elevated rates of externalizing disorders in youth at high risk for SUDs (Elkins et al., 2007), mood-related symptoms associated with these disorders are likely contributors to SUD risk. Disruptive behavior disorders are often accompanied by volatility, mood lability, and low frustration tolerance (Barkley, 1990; Skirrow et al., 2009). Such mood dysregulation is found in high-risk samples with high rates of externalizing disorders. Here, we focus on these important, but relatively neglected, emotion-related difficulties in youth at high risk for SUDs.

1.3 Neurobiological Processing of Emotional Stimuli in High-Risk Samples

Recent research on the neurobiological underpinnings of addiction risk (Cheetham et al., 2012; Glahn et al., 2007; Heitzeg et al., 2008; Wetherill et al., 2012) suggests abnormal

prefrontal hyperactivation and amygdala hypoactivation during exposure to emotional stimuli in youth at elevated familial risk for SUD. For instance, adolescents with drinking problems that were offspring of alcoholics had dorsomedial PFC hyperactivation and ventral striatal and extended amygdala hypoactivation to emotional words compared to offspring with no drinking problems and low-risk controls (Heitzeg et al., 2008). This apparent underprocessing of affective stimuli may reflect over-recruitment of a cortical emotional control system that suppresses emotional responses. Another group also found that young adults with a family history of alcoholism and high behavioral undercontrol showed impoverished amygdala activation to faces displaying negative emotions (Glahn et al., 2007).

This report aims to establish neural activation deficits during facial emotion matching prior to onset of drug use in youth at high risk for SUDs i.e., those with family SUD history and externalizing psychopathology. Drug and alcohol use undoubtedly alters the brain's maturation processes (Bava and Tapert, 2010), so we compared high- and low-risk *non-drug using* youth in the late childhood/early adolescent period that typically precedes drug experimentation. This neuroimaging study is the first to examine 1) child offspring of drug-dependent fathers (as opposed to alcoholic); 2) neural responses during a task relevant to affective processing; and 3) youth with psychopathology known to increase risk for later SUD development. This sample is the youngest investigated in an addiction risk neuroimaging study, which is important because these participants remain in the addiction risk window.

We compared familial high-risk (FHR) youth who demonstrate externalizing psychopathology and a healthy comparison (HC) group on neural activity during a well-established facial emotion processing task (Hariri et al., 2002) with functional magnetic resonance imaging (fMRI). Emotional faces are important for social interactions, and deficits in facial emotion recognition are present in high-risk youth, specifically those with conduct disorder (Fairchild et al., 2009). Based on prior studies in high-risk samples, we hypothesized that FHR youth would demonstrate lower amygdala and higher dorsomedial PFC activity when processing emotional faces, compared to controls. We supplemented our fMRI paradigm with rating scales to characterize emotion regulation deficits and hypothesized that greater severity of emotion regulation impairments would be associated with abnormal activation patterns in these regions. Specifically, we expected that covariates such as callousness and unemotionality would account for suspected amygdala hypoactivation in the FHR group.

2. METHODS

2.1 Participants

We recruited right-handed, English-speaking 10-14 year-old children with at least one parent capable of reading and speaking English. Parents were recruited from the Indianapolis metropolitan area, including addiction treatment providers, community advertisements, and contact with schools or pediatric offices. Children in, or seeking, psychiatric treatment were also recruited.

To maximize genetic risk, FHR participants were required to be biological offspring of men with past or present SUDs (excluding alcohol abuse/dependence in the absence of drug abuse/dependence), and to have an additional first or second-degree family member with SUD history. In addition to the addiction family history requirement, each FHR participant was required to meet criteria for behavioral disturbances consistent with addiction-risk models, in order to maximize risk for later addiction (Tarter et al., 2003; Zucker, 2008). Specifically, children met DSM-IV-TR criteria for attention deficit/hyperactivity disorder

(ADHD; any subtype) plus a disruptive behavior disorder defined as conduct disorder (CD), oppositional defiant disorder (ODD) or disruptive behavior disorder, not otherwise specified (DBD NOS). Use of drugs of abuse (including nicotine) or alcohol more than five times lifetime was exclusionary. Given the high probability of experimentation in this age bracket, we allowed this very limited substance experimentation.

HC participants had no current diagnosis or lifetime history of any DSM-IV psychiatric or SUDs (exceptions: specific phobias, enuresis, encopresis, learning disorders) and no first-degree relative with a history or current diagnosis of a SUD. Attempts were made to recruit groups similarly on age, race, sex, IQ, Tanner stage, and socioeconomic status.

All individuals with *in utero* exposure to drugs or alcohol, per caregiver report, were excluded. Additional exclusion criteria for both groups included bipolar disorder, psychotic symptoms, pervasive developmental disorders or SUDs; current major depressive disorder; psychopharmacologic treatment within the past 2 weeks other than psychostimulants (held the days of assessment and scanning); history of neurological problems; estimated Full-Scale IQ below 80; active or debilitating medical conditions; or MRI contraindications.

2.2 Assessment Procedures

Written consent/assent was obtained from at least one parent and the child utilizing Indiana University IRB-approved materials. Rapid urine toxicology screening (Uritox Medical) tested for five illicit drugs (methamphetamine, ecstasy, cocaine, opiates, cannabis). The substance use domain of the Drug Use Screening Inventory (Kirisici et al., 1995) was administered to each child privately.

A child-trained psychologist or psychiatrist completed the K-SADS-PL (Kaufman et al., 1997) semi-structured interview individually with parent(s) and child to determine present or lifetime psychiatric diagnoses. Parents completed checklists related to emotional functioning (described below) and Tanner staging. Children completed IQ screening (Wechsler, 1999) and the Inventory of Callous and Unemotional Traits (Roose et al., 2010).

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

To assess emotion regulation and expression differences between groups, the Expression and Emotion Scale for Children (EESC; Penza-Clyve and Zeman, 2002) and Emotion Regulation Checklist (ERC; Shields and Cicchetti, 1997) were utilized. The EESC is a reliable and consistent parent-report scale that assesses emotion awareness and expression in school-age children (Perwien et al., 2008). Subscales include "positivity," which assesses positive aspects of emotional expression, and two negative emotion subscales termed "emotional flatness" and "emotional lability." The ERC is a parent-report instrument that assesses parents' perceptions of their child's emotional expression, empathy, and emotional self-awareness, where higher scores reflect more dysregulation. Subscales include "lability/negativity," which assesses emotional lability and temper outbursts, and "emotion regulation."

The Inventory of Callous–Unemotional Traits (ICU) was collected from children (Roose et al., 2010) to ascertain the relationship of such traits to amygdala hypoactivation, given that

youth with callous and unemotional traits show deficits in processing negative emotional stimuli (Jones et al., 2009; Stevens et al., 2001).

2.3 Statistical Analyses for Behavioral/Demographic Measures

Group demographic differences were assessed using independent samples t-tests or Pearson's chi-squared tests. Pearson correlation analyses were used within each group to test the hypothesis that scores on self- and parent- report measures of emotional functioning would be associated with BOLD activation in brain regions that differed between groups on the facial emotion matching task.

2.4 Imaging Procedures

Females received a urine pregnancy test. Stimulant medications were held the morning of the scan. Urine drug screening was repeated and participants with positive screens excluded. Participants were trained on the importance of staying still in the scanner, and scans were collected by radiology technicians experienced in scanning children.

Participants were scanned on a research-dedicated 3.0 Tesla Siemens Magnetom (TIM) MRI scanner using a 32-channel head coil. After a short scout imaging scan, a high resolution 3D magnetization prepared rapid gradient echo (MPRAGE; 160 sagittal slices; $1.0 \times 1.0 \times 1.2$ mm voxel dimension) scan was acquired and used for co-registration and normalization of the functional image volumes to Talairach space. A gradient recalled echo (GRE) field-mapping scan followed (TE 4.97 ms; 7.43 ms; 39 axial slices; FOV 220×220 mm; voxel dimension $2.5 \times 2.5 \times 3.5$ mm; manually shimmed to ensure optimization of the ventral brain signal). Then, the facial emotion processing task scan was acquired using a T2*-weighted gradient echo-planar imaging (EPI) sequence (TR/TE 2250/29 ms; same slice locations and voxel dimension as GRE field mapping) using the prospective motion correction algorithm (3D-PACE, Siemens) for real-time adjustment for detected head motion. An integrated parallel acquisition technique reduction factor of 2 was implemented with a generalized autocalibrating partially parallel acquisition (GRAPPA) to improve spatial resolution, reduce geometric distortion and scan time.

2.5 fMRI Task

This block-design fMRI task (Hariri et al., 2002) reliably elicits amygdala activation across typical development (Lobaugh et al., 2006; Phillips et al., 2004). Three blocks of facial emotion matching were interleaved with four blocks of a control visual and sensorimotor shape-matching task. During the emotion matching task, subjects viewed three faces and selected one of two faces on the bottom row that express the same emotion (angry or fearful) as the target face on the top row. Each emotion block (duration= 22.5 sec) contained six unique images, three of each gender and target affect (angry or afraid), presented sequentially for 4500 ms each. During the control task, the subjects viewed three geometric shapes (vertical and horizontal ellipses) and selected one of two shapes on the bottom row identical to the target shape on the top row, with the same block and stimulus presentation time. Accuracy and reaction time were monitored during both tasks.

2.6 Image Analysis

All analyses were carried out by a trained image analyst blind to the subject's group status (TH). Only scans with less than 3.5 mm (< 1 voxel) of head displacement were included. Groups did not differ on mean head displacement (Table 1). Participants with task accuracy below chance or with questionable performance (i.e. the same button pressed for all responses) were excluded.

2.6.1 Subject-Level Analyses—Image preprocessing used AFNI software (Cox, 1996) and consisted of slice time correction, de-spiking of time series outliers (3dDespiking algorithm), motion correction via realignment to the first timepoint in the series using Fourier interpolation, registering the functional image to the structural image, correction for signal inhomogeneity with field mapping and spatial smoothing with a Gaussian kernel of 6mm full-width at half-maximum. To determine the contribution of each task to the blood-oxygen level-dependent (BOLD) signal, the block design was convolved with a hemodynamic response curve to create an ideal time series for each condition (face, shape). A general linear regression model (GLM) was created with the ideal time series, along with six motion parameters and linear and quadratic detrending terms to correct for potential scanner drift. The regression coefficients for shape and face conditions were derived for each subject. Activation was defined as the contrast of “face” and “shape” coefficients (face – shape). Activation maps were warped to a standard Talairach atlas for group analyses.

2.6.2 Group Level Analyses—Within group activation maps were separately obtained using a one-sample t-test (voxel-level $p < 0.001$, with all clusters > 54 voxels, per a Monte Carlo simulation, to correct for multiple comparisons). To test for between-group differences in face – shape activity, we carried out a one-way group (FHR, HC) ANCOVA on the parameter estimates derived from the GLM for each voxel across the two groups. We covaried for race (white, black or other), socioeconomic status (SES; defined as family income on a 1-5 scale where **1** = $< \$20,000$; **2** = $\$20,000 - < \$40,000$; **3** = $\$40,000 - < \$60,000$; **4** = $\$60,000 - < \$80,000$; **5** = $\geq \$80,000$; Table 1) and full-scale IQ, given the group differences on these variables. Multiple comparisons associated with this whole-brain voxel-wise analysis were addressed using cluster-wise thresholds. Individual voxels were considered significant at $p < 0.01$, and a Monte Carlo simulation was again used to determine that clusters > 108 voxels corrected for group level significance ($p < 0.05$). If group differences were not found in hypothesized regions (dmPFC, amygdala), region of interest (ROI) analyses using anatomical masks and small volume corrections were used.

3. RESULTS

Thirty-seven right-handed male and female participants, aged 10-14 years old completed the scanning protocol with adequate compliance. Six additional participants (4 HC and 2 FHR) who moved excessively and an additional participant (FHR) who failed to comply with task demands were excluded. Groups were matched on age, gender, head motion during scanning and Tanner stage but differed on IQ, SES and race, despite attempts to match groups on these characteristics (Table 1). Of FHR participants, 13 (68%) had taken psychotropic medications in the past and two (10%) were taking stimulants at the time of the study, which were withheld at least 12 hours prior to the scan and assessment. All HC participants were medication-naïve. For psychiatric disorders in child participants, see Table 2; for paternal SUD characteristics, Table 3.

3.1 Task Behavior and Rating Scales

All participants performed the task with a high level of accuracy. There were no group differences in reaction time or accuracy (Table 4). As expected, the FHR sample demonstrated greater impairment on all subscales of the two emotion measures and the ICU, except the ICU unemotionality subscale (Table 5).

3.2 Imaging Results

3.2.1 Within-Group Brain Activation—Both groups had bilateral activation of the amygdala, striatum, thalamus and insula, as well as the dorsolateral and medial PFC and

orbitofrontal cortex (OFC) for the face versus shapes contrast, as expected (Supplementary Table 1¹; Figure 1).

3.2.2 Between Group Activation Differences—Group activation differences on the whole-brain analysis were found in four clusters: medial PFC (Brodmann Area [BA] 10), two clusters in occipital cortex, and precuneus (Table 6). For each region, the FHR group had greater activation than the HC group on the face vs. shapes contrast (Figure 1). More specifically, HCs demonstrated deactivations with this contrast in three of the four clusters, while FHR participants showed activations. No amygdala differences were found even when using ROI masks and small volume corrections.

3.3 Relationships between Emotion Regulation and Brain Activation

We restricted these analyses to the four regions with significant group differences (Table 6). For the FHR group, mean face – shape activity in occipital cortex (Cluster D in Fig. 1) was positively correlated with self-rated impairments in emotional lability/negativity (ERC; $r = .52$, $p = .023$) and emotional flatness (EESC; $r = .48$, $p = .036$). Despite the apparent contradiction in the naming of these subscales, emotional lability/negativity and emotional flatness were correlated in the FHR group ($r = .58$, $p = 0.01$). For the HC group, no correlations were found between the emotion regulation measures and brain activation in any of the four significant clusters, although little variability was noted on these measures.

4. DISCUSSION

This study identified neurobiological differences during facial emotion processing in children at elevated genetic and phenotypic risk for the development of SUDs, prior to the onset of such drug or alcohol use. Groups were matched on age, gender, head motion and pubertal development, and analyses controlled for IQ, race and SES differences. Parent- and self-report rating scales differentiate the groups robustly, suggesting a wide range of emotion regulation deficits in FHR youth. Despite similar task performance, FHR youth demonstrated activations in medial prefrontal, precuneus and occipital cortex on the face vs. shapes contrast, while controls show deactivations within these clusters. Rating scales indexing emotional impairments correlated positively with occipital activation in the HR group only, suggesting that brain dysfunction during facial emotion processing may be related to severity of emotion regulation deficits.

The medial PFC, including BA 10 identified here, is a critical structure in a neural system sub-serving risky decision making (Bechara et al., 2005; Damasio et al., 1994; Glimcher and Rustichini, 2004), a process tightly linked to adolescent drug experimentation (Steinberg, 2008). This region has also been identified as becoming increasingly aberrant with alcohol use (Heitzeg et al., 2010). Higher mPFC activation may reflect the need for greater neuronal recruitment to compensate for deficient functioning. Thus, this investigation provides additional evidence that, consistent with our hypotheses, medial prefrontal deficits relevant to the control of affective processing, at least in the context of decision making may precede and possibly contribute to SUD development.

The “hyperfrontal” cortical control reported here is counterintuitive for youth with ADHD, given research suggesting that decreased cortical activation underlies poor regulation in ADHD (Arnsten, 2006; Konrad et al., 2006; Vaidya et al., 2005). However, our finding is consistent with other high-risk for addiction studies (Glahn et al., 2007; Heitzeg et al., 2008). Despite high rates of ADHD in these high-risk samples, this pattern of prefrontal

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*hyper*activation has been shown to differ from the *hypo*activation seen in those with ADHD and no family history of SUDs, albeit in different tasks (Ivanov et al., 2012; Whelan et al., 2012). Thus, our findings might be explained by the presence of the family history of SUDs. Alternatively, high-risk samples may contain higher levels of psychopathology, including emotional dysregulation, than pure ADHD samples and this may drive our findings. As this study design is unable to pinpoint the cause of the activation deficits (family history of addiction vs. presence of disruptive behavior disorders vs. early environment), future work is needed to disentangle the contribution of impulsive traits and a family history of addiction to brain activity in ADHD. Work in other psychiatric disorders known for behavioral dysregulation has begun to question theories of cortical hypofrontality/limbic hyperfrontality that emerged from early studies with small samples. Instead, recent meta-analytic findings across many studies demonstrate that brain activation in response to negative emotional stimuli was characterized by increased activation across a cortical network including insula and posterior cingulate, as well as decreased activation in amygdala, subgenual anterior cingulate and dorsolateral PFC (Ruocco et al., 2013).

Contrary to our hypotheses, we did not find abnormal amygdala activation in FHR youth, despite the hyperactivation seen in cortical regions with structural and functional connections with the limbic system. Amygdala activity was high in both groups, so a “ceiling effect” may have prevented detection of amygdala differences. Alternatively, given the relatively small sample, a type II error may have occurred, especially with stringent statistical thresholds used to prevent false positive findings. We maintain that amygdala activations are potentially different between these groups in some contexts, given the differences in cortical activation and their high levels of amygdala-relevant psychopathology. Additional research with different tasks can either replicate or refute the present finding.

We also report preliminary findings from several other regions that were not originally hypothesized to differ between groups. The precuneus activation differences are consistent with reported alterations in ADHD (Castellanos et al., 2008; Tomasi and Volkow, 2012). Given precuneus’ role in self-referential processing (Strauman et al., 2012) and directing visual attention (Mayer et al., 2006), these results have similar implications as occipital findings for baseline deficits that may confer risk for addiction. Namely, social failures and consequent introduction to deviant peer groups may be facilitated through impaired self-referential and visual attention processing. Such deficits have not previously been behaviorally characterized in high-risk samples or included in models of addiction development, although precuneus function is impacted by drugs of abuse (Hartwell et al., 2011; Warbrick et al., 2012). This work suggests more focus is needed on the intersection between complex cognitive-affective processing involving attention to visual and social information, such as one’s role in social interactions.

The higher occipital activity that we report in the FHR group has been reported in other psychiatric samples responding to facial stimuli (Davidson et al., 2003; Thomas et al., 2012). The visual regions differentially activated between our groups, (Figure 1, clusters C & D), do overlap with the occipital face region. This region, in conjunction with subcortical regions such as the amygdala, provides facial feature information to primary visual cortex in humans (Petro et al., 2013; Pitcher et al., 2011). As with our mPFC findings, we speculate that occipital cortex inefficiencies may require greater activation to accomplish facial emotion processing in high-risk youth. Impoverished facial feature processing, perhaps driven by occipital deficits, have significant implications for emotion regulatory and interpersonal capabilities and, in turn, social marginalization and possibly drug use (Hill et al., 2007). In addition, human electrophysiological studies suggest that amygdala potentials

spread first to occipital cortex (Krolak-Salmon et al., 2004), so between-group differences may be larger here, relative to other cortical regions.

While our task examined brain activation specific to facial emotion matching, emotion regulation deficits not assessed by this task may actually be more relevant to drug use initiation and progression (Berking et al., 2011). Deficits in emotional functioning, in the form of baseline negativity/flatness and labile responses, were positively correlated with occipital cortex activity in the FHR group. These deficits in emotion regulation have been related to frontolimbic circuit activity (Fulwiler et al., 2012; Hulvershorn et al., 2011), further suggesting that occipital differences are driven by aberrant projections from this circuit. These elevations in regulation, lability and flatness scores may reflect FHR youths' chronic irritability, including baseline affective negativity and quickness to respond with extreme affect when provoked. One hypothesis explaining the trajectory from childhood affective impairments to later SUDs asserts that weak social interactions resulting from extreme affective responses result in peer marginalization, fewer social opportunities, and social avoidance (Tarter et al., 1995). As opportunities for normative social interactions diminish, options become confined to socializing with deviant or marginalized individuals who tolerate and exhibit similar response patterns.

Despite the advantages of this sample over those of similar neuroimaging studies, several limitations must be noted. This study design is based on the assumption that externalizing psychopathology in offspring of males with SUDs accurately assesses risk for the development of SUDs. This model has not been tested in females and does not have predictive validity in non-white participants, due to limited power in longitudinal studies (Tarter et al., 2004, 2003). It remains to be seen if FHR youth in this sample will develop SUDs at higher rates than controls. Second, to screen out those with more than five lifetime uses we relied on self-report of substance use, which may be inaccurate. Third, most FHR participants have taken psychotropic medications, raising the possibility that brain activation may be impacted by factors other than addiction risk. Fourth, groups differed on several demographic factors, including lower SES, lower IQ and predominant African American race in the FHR group. Substantial efforts were made to recruit similarly matched control participants, but, as with similar designs (Serec et al., 2012; Tarter et al., 2003), paternal SUDs across generations appear to create downward social drift more powerfully than factors which might also affect potential low-risk families. While imaging analyses controlled for these variables, they may impact our results. Fifth, because disruptive behavior disorders and a family history of SUDs are completely overlapping in our FHR group and not present at all in the HC group, we are unable to attribute the etiology of our findings specifically to either factor. Finally, because the anxious and angry faces were displayed within the same block in this task, we cannot examine activation in response to specific emotions.

Our data support the growing need to examine affective processing in high-risk youth prior to extensive substance use. Aberrant brain activation in regions relevant to risky decision-making and social cognition appears to predate established drug use. Future work following high-risk samples into mid-adolescence can aid in identifying biomarkers predictive of SUD development, as well as the impact of drugs of abuse on brain development. This work also has the potential to inform evolving addiction prevention and treatment efforts for high-risk youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Within-group activation and between-group differences for face – shape contrast
 The first two columns show healthy comparisons (HC; N=18) and familial high-risk (FHR; N=19) within-group contrasts (face – shape) of coefficients. The X value represents the Talairach coordinate for the sagittal slice. Activation maps show significant voxels only ($p < 0.001$; cluster size $k > 50$ voxels). Orange/yellow indicates higher activity during face blocks, blue indicates lower activity during face blocks. Group differences (FHR - HC) of this face – shape contrast were seen for four regions (A-D) circled in red in the third column. For these between-group contrasts, orange represents clusters with significantly greater face – shape activity in the FHR group ($p < 0.01$; $k > 108$). Box plots show the distribution of mean face – shape contrast within each cluster. Boxplots show each interquartile range (colored box), along with minimum and maximum (bars) and the median. No outliers are present.

Table 1

Demographic, head motion and drug use information by group.

	FHR (n = 19)	HC (n = 18)	P
Number of Females (%)	5 (26%)	7 (39%)	0.414
Age	12.2 (1.4)	11.9 (1.4)	0.519
<i>Race</i>			
Caucasian	5 (26%)	12 (67%)	0.014
African American	13 (68%)	5 (28%)	0.013
Other	1 (5%)	1 (6%)	0.969
IQ	98.2 (10.5)	111.8 (9.3)	< 0.001
SES: Parental Work (# hours/week)	2.0 (2.2)	4.56 (1.3)	< 0.001
SES: Family Income	1.58 (0.9)	4.22 (1.3)	< 0.001
Tanner Stage	2.4 (0.7)	2.2 (0.9)	0.471
MRI Head Displacement (mm)	0.213 (0.06)	0.193 (0.04)	0.240
Participants with any drug use	3 (15.8%)	0 (0%)	0.083
Total number of drug use instances	5	0	0.167

Table 2

DSM-IV diagnoses by group.

FHR Group (n=19)	Present Disorders	Past Disorders
ADHD, Combined Type	18	19
ADHD, Inattentive Type	1	0
ADHD, NOS	0	0
Conduct Disorder	1	0
ODD	15	16
Disruptive Behavior Disorder NOS	3	3
Generalized Anxiety Disorder	3	3
Separation Anxiety Disorder	2	2
Social Anxiety Disorder	1	1
Anxiety Disorder NOS	2	2
PTSD	0	1
Adjustment Disorder	0	3
Major Depressive Disorder	0	3
Depressive Disorder NOS	1	1
Enuresis	2	5
Specific Phobia	0	0
Eating Disorder NOS	0	0
HC Group (n=18)		
Enuresis	0	1
Specific Phobia	1	1
Eating Disorder NOS	0	1
Depressive Disorder NOS	0	1

Table 3

Paternal substance use among familial high risk youth (n=19).

	<u># of Fathers Diagnosed</u>	<u>% of Fathers with Diagnosis</u>
Alcohol Dependence	14	73.7
Alcohol Abuse	1	5.3
Cannabis Dependence	11	57.9
Cannabis Abuse	4	21.1
Cocaine Dependence	7	36.8
Hallucinogen Dependence	1	5.3
Opiate Dependence	6	31.6
Opiate Abuse	1	5.3
Sedative Dependence	1	5.3
Polysubstance Dependence	4	21.1
Number of SUD Diagnoses Per Individual	# of Individual Fathers	% of Total Fathers
1 SUD diagnosis	4	21.05
2 SUD diagnoses	1	5.26
3 or greater diagnoses (includes polysub.)	14	73.68

Table 4

Accuracy across conditions (faces and shapes) and reaction time (RT) across conditions for all trials (all resp) and for all correct trials (correct).

	High Risk (n=19)	Low Risk (n=18)	P
Shape Accuracy	90.26% .01	94.39% .08	0.177
Face Accuracy	72.31% .13	73.84% .13	0.717
Shape RT – correct	1072.66 269.79	990.6878 183.77	0.290
Face RT – correct	2049.99 484.53	2025.80 268.43	0.853
Shape RT – all resp	1057.68 268.49	978.55 188.51	0.309
Face RT - all resp	2062.21 485.35	2027.08 239.25	0.784

Table 5

Scores (mean and standard deviation (SD)) on measures of emotion regulation, for familial high-risk (FHR) and healthy comparison (HC) participants.

Measure	Group	Mean (SD)	t	p
Emotion Regulation Checklist				
Lability/Negativity	FHR	37.1 (8.1)	−8.69	<0.001*
	HC	19.2 (3.2)		
Emotion Regulation	FHR	22.6 (4.2)	5.69	<0.001*
	HC	28.9 (2.3)		
Emotional Expression Scale for Children				
Positivity	FHR	35.9 (9.8)	−3.67	0.001*
	HC	25.9 (6.3)		
Negativity: Flatness	FHR	22.3 (7.8)	−5.25	<0.001*
	HC	12.1 (2.9)		
Negativity: Emotional Lability	FHR	16.4 (4.5)	−7.81	<0.001*
	HC	7.1 (2.4)		
Inventory of Callous and Unemotional Traits				
Callousness	FHR	9.2 (4.8)	−2.27	0.029*
	HC	5.8 (4.2)		
Uncaring	FHR	11.0 (5.1)	−4.27	<0.001*
	HC	5.1 (2.8)		
Unemotional	FHR	7.2 (2.1)	−1.64	0.109
	HC	6.0 (2.1)		

Table 6

Significant activation differences between groups on the face versus shape contrast.

Region	BA	Peak t Value	p Value	Cluster Size	Talairach Coordinates		
					X	Y	Z
A. R Medial Prefrontal Cortex	10	3.88	0.0007	128	9	59	22
B. L Precuneus	7	4.02	0.0005	164	-9	-77	42
C. L Mid Occipital Gyrus	18	4.34	0.0002	186	-21	-91	14
D. R Mid Occipital Gyrus	19	4.73	0.00008	240	39	-73	20