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Emotional Processing and Brain Activity in Youth at High Risk for Alcoholism

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Abstract

Background—Even in the absence of heavy alcohol use, youth with familial alcoholism (family history positive [FHP]) exhibit atypical brain functioning and behavior. Although emotional and cognitive systems are affected in alcohol use disorders (AUDs), little attention has focused on whether brain and behavior phenotypes related to the interplay between affective and executive functioning may be a premorbid risk factor for the development of AUDs in FHP youth.

Methods—Twenty-four FHP and 22 family history negative (FHN) 12- to 16-year-old adolescents completed study procedures. After exclusion of participants with clinically significant depressive symptoms and those who did not meet performance criteria during an Emotional Go-NoGo task, 19 FHP and 17 FHN youth were included in functional magnetic resonance imaging (fMRI) analyses. Resting state functional connectivity MRI, using amygdalar seed regions, was analyzed in 16 FHP and 18 FHN youth, after exclusion of participants with excessive head movement.

Results—fMRI showed that brain activity in FHP youth, compared with FHN peers, was reduced during emotional processing in the superior temporal cortex, as well as during cognitive control within emotional contexts in frontal and striatal regions. Group differences in resting state amygdalar connectivity were seen bilaterally between FHP and FHN youth. In FHP youth, reduced resting state synchrony between the left amygdala and left superior frontal gyrus was related to poorer response inhibition, as measured during the fMRI task.

Conclusions—To our knowledge, this is the first study to examine emotion–cognition interactions and resting state functional connectivity in FHP youth. Findings from this research provide insight into neural and behavioral phenotypes associated with emotional processing in familial alcoholism, which may relate to increased risk of developing AUDs.

Keywords

Alcoholism; Emotion; Family History; fMRI; Resting State

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

ALCOHOL USE DRAMATICALLY increases during adolescence and is a major health burden to the individual and society. While several factors are associated with increased risk of heavy drinking during this period, family history of alcohol dependence significantly raises alcohol use disorder (AUD) risk (Goodwin, 1985). Therefore, identifying behavioral and neural features of familial alcoholism is critical to understanding risk of developing an AUD.

Deficits in executive functioning behavior and/or brain activity have often been examined in family history positive (FHP) youth, with studies generally pointing to atypical cognitive functioning even in the absence of alcohol abuse (Corral et al., 1999; Cservenka and Nagel, 2012; Schweinsburg et al., 2004). However, emotional processing and its relationship with cognition have received less attention. Research suggests that nonalcohol-abusing FHP individuals share similar deficits in affective systems to alcohol abusers, including reduced amygdalar volume and activity in response to emotional stimuli (Glahn et al., 2007; Hill et al., 2001; Marinkovic et al., 2009; Wrase et al., 2008). Furthermore, affective measures, such as subclinical depressive symptoms, in FHP alcoholics also relate to deficits in executive functioning, on verbal, problem-solving, perceptual motor, and learning tasks (Sinha et al., 1989). This indicates that familial history of AUDs may put individuals at greater risk for problems with emotional processing, which could in turn negatively impact executive functioning (Sinha et al., 1989) and increase risk for alcohol abuse. Emotion and cognition have often been found to be integrated in dorsolateral prefrontal cortex (PFC) during emotion–cognition tasks (Pessoa, 2008), suggesting that affective information could interfere with executive functioning brain response through structural and functional connections between the amygdala and PFC.

To our knowledge, no studies of FHP youth have examined brain activity and behavior related to emotional processing and the interplay with executive functioning. This investigation is essential, because parental alcoholism is associated with emotional dysregulation and risk for affective problems in children (Christensen and Bilenberg, 2000). Accordingly, negative affect has been shown to mediate the relationship between familial alcoholism and risk taking, the latter of which is significantly related to substance use (Ohannessian and Hesselbrock, 2008). Recently, functional magnetic resonance imaging (fMRI) in heavy-drinking FHP adolescents found atypical brain activity in frontal and limbic areas in response to verbal emotional stimuli (Heitzeg et al., 2008) and blunted brain activity during a theory of mind paradigm in brain regions implicated in social evaluation (Hill et al., 2007). Additionally, youth with a family history of substance use disorders (mainly alcohol and cannabis dependence) and present externalizing psychopathology showed hyperactivation in occipital and frontal lobe regions during an emotion-matching task (Hulvershorn et al., 2013). However, it is still unclear whether typically developing FHP adolescents, free of psychopathology, may already show similar features in brain response to FHP adults and alcoholics, in the absence of alcohol-induced neurotoxicity. To help answer this question, we implemented a modified Emotional Go-NoGo fMRI task. Based on existing data in FHP individuals, we hypothesized that FHP youth would have blunted amygdalar response to negative emotional expressions. In addition, given documented underpinnings of inhibitory control during adolescence (Rubia et al., 2006), we expected

reduced brain activity in dorsolateral prefrontal, inferior frontal, and dorsal anterior cingulate cortices in FHP youth during cognitive control in an emotional context.

Furthermore, to better characterize the relationship between affective and cognitive control circuitry in youth at risk for alcoholism, we also employed resting state functional connectivity magnetic resonance imaging (rs-fcMRI). As rs-fcMRI can provide information about the integrity of brain networks without task-related demands, it has been increasingly used to complement existing knowledge about brain functioning from classical fMRI task paradigms, as it closely corresponds to task-related fMRI blood oxygen level-dependent (BOLD) signal, and behavioral performance (Fox et al., 2007; Smith et al., 2009). Investigating limbic and executive functioning using both task-related fMRI and rs-fcMRI could provide complementary information on brain activity and behavioral performance relationships. Importantly, many recent resting state connectivity studies are aiming to understand whether the intrinsic BOLD signal has any association with task performance (i.e., Koyama et al., 2011), thereby examining the relevance of brain network architecture to human behavior. Given evidence of atypical resting state functional connectivity in limbic and executive control regions in alcoholics (Camchong et al., 2013), the question remains as to whether these may be premorbid characteristics in at-risk youth. Recent task-related functional connectivity studies have shown premorbid abnormalities in FHP youth (Herting et al., 2011; Wetherill et al., 2012). However, there has only been 1 published study, to date, of rs-fcMRI in FHP youth (Cservenka et al., 2014), but no studies examining the integrity of affective circuitry. Based on the findings of both atypical executive control and limbic circuitry in alcoholics and FHP youth, we hypothesized that FHP youth would show reduced connectivity between the amygdala and brain regions important for executive control and that this would relate to response inhibition during a task examining emotion–cognition interactions.

MATERIALS AND METHODS

Participant Recruitment and Exclusionary Criteria

Adolescents, 12 to 16 years old, were recruited from the community. Parent informed consent and youth assent forms were obtained from all participants. Previously reported exclusionary criteria (Cservenka and Nagel, 2012), including major medical or Axis I psychiatric conditions, were used to determine study eligibility. As the purpose of this study was to examine family history of alcoholism and emotional processing without confounds of heavy substance use, youth who reported lifetime alcohol use of >10 drinks or >2 drinks/occasion, >5 uses of marijuana, >4 cigarettes per day, or any other drug use were excluded (Brown et al., 1998). All procedures were approved by the Oregon Health & Science University (OHSU) Institutional Review Board.

Participant Characterization

A modified version of the Family History Assessment Module (Rice et al., 1995) that included second-degree relatives was used to characterize youth as FHP or family history negative (FHN). Based on family history classification criteria previously described in detail (Cservenka and Nagel, 2012), 24 FHP and 22 FHN youth completed study visits. Family

history density (FHD) or the degree of familial alcoholism was calculated for each FHP youth by considering the contribution of AUDs from first- and second-degree relatives (Cservenka and Nagel, 2012). To estimate intelligence levels, the 2-subtest Wechsler Abbreviated Scale of Intelligence was administered to all participants (Wechsler, 1999). Additional questionnaires used to characterize the groups included the Perceived Stress Scale (Cohen et al., 1983), the Inventory of Callous-Unemotional Traits (Frick PJ, unpublished data), the Children's Depression Inventory (CDI; Kovacs, 1985), and the UPPS-P Impulsive Behavior Scale for Children (Zapolski et al., 2010). Self-assessment of pubertal status was determined using a modified line drawing version of the Tanner's Sexual Maturation Scale (Taylor et al., 2001). The Hollingshead Index of Social Position (Hollingshead, 1957) was administered to each participant's parent to compare socioeconomic status between FHP and FHN youth.

Functional Magnetic Resonance Imaging

Emotional Go-NoGo Task—Participants completed a modified version of the previously published Emotional Go-NoGo task (Fig. 1; Hare et al., 2008) in E-Prime Version 1.1 (www.pstnet.com/eprime.cfm). Four runs were performed in the scanner with happy, scared, or calm target faces (go trials) and calm nontarget faces (nogo trials). The ratio of go to nogo stimuli was 70/30 percent for each run of the task (Somerville et al., 2011). Two runs with happy or scared go stimuli consisted of 60 go/26 nogo faces. Two other runs included only calm faces: male go/female nogo, and female go/male nogo. Each of these runs had 30 go and 13 nogo trials that were concatenated, resulting in 60 calm go trials and 26 calm nogo trials. All stimuli were presented for 500 ms, with interstimulus intervals jittered between 2,000 and 12,000 ms, as determined optimal by Freesurfer's (Fischl, 2012) OptSeq (<http://surfer.nmr.mgh.harvard.edu/optseq/>), an fMRI experiment timing and optimization tool. Only calm nontarget faces (CalmNoGo) were selected for nogo trials, because this study was aimed at examining cognitive control during emotional (HappyGo or ScaredGo faces) and nonemotional (CalmGo faces) contexts. Additionally, calm faces were specifically selected as opposed to neutral faces because children have been shown to respond differently to neutral faces than adults (Thomas et al., 2001). Further details on the task and results of the exit questionnaire following the scan are included in Data S1 and Table S1.

Behavioral Data Analyses—In each group, dependent variables were inspected for normality using Shapiro–Wilk tests, kurtosis, and skewness examinations. Demographic and personality variables were compared between groups with independent-samples *t*-tests, Mann–Whitney *U*-tests, or chi-square tests, when appropriate. Participants who completed all 4 runs of the Emotional Go-NoGo task and met the performance criteria (14 correct rejections on nogo trials during the presentation of happy, scared, or calm target faces) to have sufficient data for modeling the hemodynamic response function (HRF) were included in the fMRI analyses, resulting in 19 FHP and 17 FHN youth. Emotional Go-NoGo task behavioral data were analyzed using a mixed model multivariate analysis of variance (MANOVA), with reaction time, hits, correct rejections, and *d*-prime as within-subjects measures, and family history status as the between-group variable. Statistical analyses were carried out in SPSS Statistics version 20.0 (IBM, Armonk, NY), while bar graphs and plots

were created in Graph-Pad Software version 5.04 for Windows (GraphPad Software, La Jolla, CA, www.graphpad.com).

Image Acquisition—MRI took place on a 3T Siemens Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany) at OHSU's Advanced Imaging Research Center with a 12-channel head coil. Prior to the fMRI task, a T1-weighted anatomical magnetization-prepared rapid acquisition with gradient echo sequence (Cservenka and Nagel, 2012) was acquired for coregistration of functional data to each participant's brain anatomy. T2* BOLD imaging was used to collect fMRI data during 4 runs of the Emotional Go-NoGo task (time to repetition [TR] = 2,000 ms, time to echo [TE] = 30 ms, flip angle = 90°, resolution = 3.75 × 3.75 × 3.8 mm, field of view (FOV) = 240 mm², 33 slices). Runs with emotional go and calm nogo trials included 237 TRs (~8:00 minutes each), while runs with only calm target (go) and distractor (nogo) faces included 119 TRs (~4:00 minutes each). Total time for task acquisition was ~24 minutes.

Image Preprocessing—Standard image preprocessing steps were performed using Analysis of Functional NeuroImages (AFNI; Cox, 1996) to correct for slice timing, linear drift, motion, and artifact, as well as generate an anatomical mask for each participant (Data S1). Then, using AFNI's 3dREMLfit, a general linear model was used to estimate the BOLD response for each of the 6 regressors of interest (HappyGo, ScaredGo, CalmGo, and CalmNoGo in the 3 different target emotional contexts) on correct go and correctly inhibited nogo trials. Misses on go and false alarms on nogo trials were included as regressors of no interest, along with the 6 translational and rotational motion parameters. Stimulus onset times were entered for each of the regressors of interest, which were convolved with the one-parameter gamma-variate function to model the HRF for each individual. Functional data were resampled into 3 mm³ voxels and transformed to standardized Talairach space (Talairach and Tournoux, 1988).

Image Analyses—Following the preprocessing steps, group analyses were performed to compare whole-brain activity for FHP and FHN youth on the contrasts of interest. The contrasts examined for go trials included HappyGo versus CalmGo and ScaredGo versus CalmGo (brain response to emotional faces). The contrasts for CalmNoGo trials included HappyGo(CalmNoGo) versus CalmGo (CalmNoGo) and ScaredGo(CalmNoGo) versus CalmGo(CalmNoGo) (for examination of the impact of emotional context on cognitive control). While nogo versus go contrasts are often examined to investigate inhibitory control, there is evidence that target frequency presentation alone can influence brain response, making it difficult to distinguish inhibitory control from stimulus frequency presentation and nogo trial novelty (Casey et al., 2001). For this reason, nogo versus go brain activity was not examined in the current study. First, task-related activity in each group was examined with 1-sample *t*-tests for each contrast of interest ($p/\alpha < 0.05$, 205 voxels; Data S1). Next, individual group maps for FHP and FHN (voxel thresholded at $p < 0.05$) were added together to comprise the task-related activity map. Independent-samples *t*-tests compared groups on brain response within these task-related activity maps for each contrast of interest. AFNI's AlphaSim Monte Carlo simulation was used to correct for multiple comparisons with a voxel ($p < 0.01$) and cluster ($\alpha < 0.05$) threshold (Forman et al., 1995).

Additionally, a region of interest (ROI) analysis was performed on the left and right amygdala to examine group differences in brain activity to emotional faces. FMRIB Software Library's Integrated Registration and Segmentation Tool (Patenaude et al., 2011) was used to delineate each participant's left and right amygdala, which were subsequently visually inspected. ROI analyses were masked by the task-related contrasts of interest (brain response to emotional faces), followed by Monte Carlo multiple comparison correction in these group difference masks. A less stringent voxel/cluster correction ($p/a < 0.05$, 16, and 15 contiguous voxels for the left and right amygdalar ROI, respectively) was used.

Resting State Functional Connectivity Magnetic Resonance Imaging Rs-fcMRI

Image Acquisition—Resting state data were acquired over 2 runs (TR = 2,500 ms, TE = 30 ms, flip angle = 90°, resolution = $3.75 \times 3.75 \times 3.8$ mm, FOV = 240 mm², 36 slices, 100 TRs, time of acquisition for each run: 4:17 minutes). Participants were instructed to lie still and fixate on a white crosshair in the middle of a black screen.

Image Preprocessing and Analyses—Resting state data preprocessing followed common procedures (Fair et al., 2009) used to reduce spurious noise unlikely due to neuronal activity that may cause artifact and affect the spontaneous BOLD fluctuations of interest (Data S1). Connectivity maps were generated by correlating the time course of the amygdalar ROIs with all other voxels in the brain. A 2-sample *t*-test (assuming unequal variance $p < 0.05$) compared whole-brain differences between FHP and FHN youth (comparing the Fisher *Z*-transformed *r*-values). Monte Carlo simulation was applied for multiple comparison correction ($p < 0.05$, $Z > 2.25$, 53 voxels).

RESULTS

Participant Characteristics for fMRI

Nineteen FHP and 17 FHN youth met the minimum performance criteria on the Emotional Go-NoGo task to be included in the fMRI analyses. The groups did not differ on any of the demographic (Table 1) or personality variables (Table S2).

Emotional Go-NoGo Task Behavior

Behavior on the Emotional Go-NoGo task is reported in Table 2. A significant multivariate effect of Emotion was found, $F(8, 27) = 7.41$, $p = 0.00$, partial $\eta^2 = 0.69$, but there were no significant Group or Emotion $\times$ Group effects. These results did not change, even when examining behavior for the initial sample (24 FHP, 18 FHN; 2 FHN excluded due to ≤ 5 T-score on the CDI to rule out clinically significant depressive symptoms that could confound interpretation, and another 2 FHN excluded because task instructions were not followed) of participants, prior to excluding youth with poor task performance. Given the lack of Group or Group $\times$ Emotion effects, no behavioral covariates were included in the imaging analysis. The effect of Emotion was examined on hits, correct rejections, reaction time, and d-prime using mixed model ANOVAs (Data S1).

Emotional Go-NoGo Brain Activity

Prior to examination of group differences, task-related brain activity was analyzed for each group using 1-sample *t*-tests (Figs S1 and S2, Tables S3 and S4).

Between-group differences in brain response to emotional faces and inhibitory control are reported in Table 3. There were significant group differences in brain activity to positively valenced faces (HappyGo vs. CalmGo), but not negatively valenced faces (ScaredGo vs. CalmGo). Specifically, FHP youth showed less activity to happy faces in 2 clusters, including areas of the left superior temporal gyrus (STG), left insula, and left postcentral gyrus (Fig. 2). Emotion $\times$ Group interactions were present in these regions (cluster 1: $p < 0.01$, partial $\eta^2 = 0.29$; cluster 2: $p < 0.01$, partial $\eta^2 = 0.36$). There were no significant group differences in response to negatively valenced faces. Independent-samples *t*-tests indicated no significant group differences in amygdalar activation in either of the contrasts comparing brain response to emotional faces.

Significant differences in brain activity during cognitive inhibitory control in FHP and FHN youth are illustrated in Fig. 3. During response inhibition (CalmNoGo trials) in both the positively and negatively valenced emotional context, FHP youth showed deactivation compared with FHN youth (Table 3 and Fig. 3). The majority of these clusters were in regions implicated in cognitive control (frontal and parietal), with the exception of the parahippocampal gyrus (Table 3 and Fig. 3B). Mixed model ANOVAs showed a significant interaction between Emotion and Group in all 9 clusters (all $ps < 0.01$, partial η^2 range = 0.23 to 0.49). Examination of simple effects indicated that in all of these regions, FHP youth had reduced brain response during inhibition (CalmNoGo trials) when target faces were emotionally valenced compared with FHN youth ($ps < 0.05$). Additionally, in 3 of the 7 clusters FHP youth showed more activity during response inhibition when calm target faces were present compared with their peers ($ps < 0.05$). There was a significant negative relationship between FHD and BOLD activity in the left middle frontal gyrus (cluster 5 in Fig. 3B) in the negative emotional context ($R^2 = 0.42$, $\beta = -0.65$, $p = 0.003$).

Participant Characteristics for Resting State Functional Connectivity

Sixteen FHP and 18 FHN adolescents were included in rs-fcMRI analyses. Groups were very well matched on mean percentage frames removed, variance in signal intensity, and frame-to-frame displacement (Table 4), as well as demographic (Table 5) and personality characteristics (Table S5). This sample was selected from the 24 FHP and 20 FHN who completed resting state scans (excluding 2 FHN youth with > 65 CDI scores) and was not limited to those youth who had adequate number of TRs to be included in the task-based fMRI analysis. Instead, exclusionary criteria were solely based on movement thresholds, and in 1 case, data preprocessing errors, also likely due to significant head movement.

Whole-Brain Amygdalar Resting State Functional Connectivity

Using a whole-brain analysis, 7 clusters showed group differences in left and 3 regions differed in right amygdalar functional connectivity between FHP and FHN youth (Table 6). Specifically, FHP and FHN youth differed in left amygdalar connectivity with 2 clusters in the left superior frontal gyrus (SFG), 1 in the right MFG, 2 in the cerebellum, 1 in the left

precuneus, and 1 in the right precentral gyrus. They also differed in right amygdalar functional connectivity with the right MFG, right cerebellum, and right middle temporal gyrus (MTG; Fig. 4).

Resting State Functional Connectivity and Task Behavior Relationships

Next, we investigated whether differences in amygdalar connectivity were related to behavioral phenotypes. As the Emotional Go-NoGo task required participants to exert inhibitory control during trials embedded in different emotional contexts, limbic and prefrontal control networks may be important for execution of this task. Thus, the number of correct rejections during the Emotional Go-NoGo task was correlated with the correlation coefficients (r -values) between the amygdala and PFC ROIs in which group differences in connectivity were observed.

For correct rejections during the positively and neutrally valenced emotional contexts, greater segregation (or negative connectivity) between the amygdala and SFG was related to poorer inhibitory control (fewer correct rejections; HappyGo/CalmNoGo: $r = 0.72$, $p = 0.002$ [Fig. 5]; CalmGo/CalmNoGo: $r = 0.66$, $p = 0.005$ [Fig. S3]; corrected for False Discovery Rate, $p < 0.05/2$) in FHP youth, and this association was trend-level relationship for the negatively valenced emotional context ($r = 0.46$, $p = 0.07$ [Fig. S3]).

To further clarify this relationship, correct rejections from each of these task conditions were used as a predictor of left amygdalar resting state connectivity in the FHP group. Better inhibitory control during the HappyGo/CalmNoGo run was predictive of increased connectivity between the left amygdala and left SFG (Monte Carlo corrected, $p < 0.05$, $Z = 2.25$, 53 voxels). A conjunction analysis indicated that a cluster (11 voxels) showed significant group differences in connectivity and was also related to task performance in FHP youth.

DISCUSSION

The aim of this study was to investigate emotional processing and its association with inhibitory control in FHP and FHN youth, in the absence of heavy alcohol use. We found that FHP and FHN youth showed significant differences in brain response to emotional faces and different patterns of brain activity during cognitive control embedded within emotional contexts. Furthermore, the left and right amygdala had altered patterns of resting state connectivity in FHP youth compared with their peers, and this was related to inhibitory control performance on the Emotional Go-NoGo task.

Task-Based fMRI

Brain Response to Emotional Faces—Surprisingly, the ROI analysis of the amygdala indicated that FHP youth did not show different neural response to either scared or happy faces compared with their peers. This lack of significant finding may be due to various population and task-related factors, such as type of control stimulus used (calm face vs. geometric shapes), task design (go/nogo vs. emotion matching; Glahn et al., 2007), amygdala definition (automatic segmentation vs. peak coordinate of activation), and potentially inadequate power, due to the moderate sample size of the groups. Furthermore,

the findings in FHP adults and alcoholics may reflect a direct influence of alcohol use on amygdalar reactivity, because in these studies even FHP adults had multiple experiences with heavy alcohol use. Given evidence of structural alterations in the amygdala in alcohol abusers (Wrase et al., 2008), it is plausible that reactivity of this region may change largely as a result of alcohol neurotoxicity.

Despite the lack of ROI group differences, FHP youth did show significantly reduced brain activity to happy faces in the STG, which has been implicated in face perception during fMRI tasks (Narumoto et al., 2001) and supports previous findings of atypical emotional response in the right MTG in FHP adults (Hill et al., 2007). Blunted activity in this region in FHP youth is interesting given evidence of reduced activity in this area during emotion discrimination in individuals with high levels of social anhedonia (Germine et al., 2011). The current findings may suggest possible premorbid neural markers of altered socioemotional processing in FHP youth, a deficit previously reported in alcoholics (Thoma et al., 2013).

Cognitive Control Brain Activity in Emotional Contexts—FHP youth displayed widespread fronto-parietal deactivation during response inhibition in both positive and negative emotional contexts. These findings support previous studies that reported reduced executive function brain activity in FHP adolescents during fMRI tasks (Cservenka and Nagel, 2012; Schweinsburg et al., 2004), but are opposite to findings of inhibitory control activation in other studies of familial alcoholism (DeVito et al., 2013; Heitzeg et al., 2010; Kareken et al., 2013; Silveri et al., 2011). Differences may be due to previous examination of FHP adults, use of cognitive tasks that did not include emotional stimuli, problem drinking in FHP youth previously examined, the contrast of interest (nogo in different emotional contexts in the current study vs. nogo > go brain activity in previous work), as well as the acute effects of alcohol intoxication on inhibitory control brain activity (for comparisons, see DeVito et al., 2013; Heitzeg et al., 2010; Kareken et al., 2013). Interestingly, despite no significant differences in brain activity to scared faces in FHP and FHN youth, the impact of these target faces on executive control was still observed. In the caudate nucleus, involved in inhibitory control (Rubia et al., 2006), FHP youth showed reduced activity during nogo trials when negatively valenced target faces were present compared to their peers. However, they showed positive activation in this region when inhibition took place in the nonemotional context. This could suggest that while FHP youth may still have the cognitive resources to activate this brain region during response inhibition in “cool” situations, their executive resources are derailed when emotions become involved, such as in “hot” social situations. Future work is needed to expand these results and examine cortico-limbic system development in FHP youth to better explain how emotional processing may interfere with top-down control, instead of limiting the focus on deficits present purely in “cold” executive functioning skills where no affective component is present.

Resting State Functional Connectivity and Task Behavior Relationships

A growing literature has examined functional connectivity of brain regions in alcoholics and FHP adolescents and has found atypical patterns of connectivity in these individuals (Camchong et al., 2013; Herting et al., 2011; Wetherill et al., 2012). However, most of the

research has used task-based functional connectivity analyses (Herting et al., 2011; Wetherill et al., 2012), with only 1 rs-fcMRI study reported in FHP youth (Cservenka et al., 2014). This approach is important, as developmental studies have shown that brain networks develop from local to more distributed connections across age (Fair et al., 2009), suggesting more integrative communication among anatomically distant brain areas with development.

Our results indicated that using the whole-brain rs-fcMRI approach, FHP youth showed reduced functional connectivity between the amygdala and 4 bilateral PFC areas (SFG and MFG) compared with their peers. The regulatory role of PFC areas in cognition is well established (Rubia et al., 2006), suggesting that the current findings may indicate a reduced capacity of PFC control over limbic structures, such as the amygdala, in at-risk youth. Recently, Qin and colleagues (2012) reported that healthy children show reduced integration of resting state connectivity between the amygdala and prefrontal cortices compared with adults. It is possible that FHP youth have weaker or more developmentally delayed connectivity between these areas. However, there are conflicting findings of amygdalar resting state patterns with other brain regions. For example, in contrast to Qin and colleagues' (2012) study, others have reported negative functional connections between the amygdala and dorsal PFC, albeit this study was conducted in adults (Roy et al., 2009). To clarify brain and behavior relationships, the analysis in the current study indicated that in FHP youth, greater connectivity of the left SFG and amygdala was significantly associated with fewer task-related inhibitory commission errors. This suggests that the anticorrelated pattern of left amygdala-left SFG connectivity may be maladaptive in at-risk adolescents, as shown by a direct behavioral correlate of this resting state pattern.

One of the most unique patterns of connectivity was observed in the cerebellum, in which FHP youth not only showed significant differences from their peers, but displayed opposite functional connections with the amygdala. Other studies in FHP youth also found atypical functional connections with the cerebellum, including reduced fronto-cerebellar connectivity (Herting et al., 2011), and alterations in nucleus accumbens and cerebellar connectivity (Cservenka et al., 2014). The cerebellum, while classically implicated in motor control, is likely also involved in emotional processing, as electrical stimulation of the cerebellum results in neuronal firing in the amygdala (Heath et al., 1978). This implies that amygdala and cerebellum resting state synchrony is functionally plausible, but more work is needed to understand cerebellar abnormalities in FHP individuals and the risk they represent for alcohol abuse. Given findings of atypical fronto-, accumbens-, and amygdalar-cerebellar connectivity in FHP youth, future work should examine cerebellar network characteristics in FHP youth, using graph theory approaches, in addition to seed-based analyses.

Interpretations from fMRI and rs-fcMRI

The examination of the task-based findings showed that inhibition within emotional contexts impacts fronto-parietal circuitry in FHP youth, reducing cognitive control brain response in this group compared with their peers. Further, the findings at rest showed that the integrity of affective and cognitive circuitry is altered in FHP youth, as these adolescents had more asynchronous connectivity between the amygdala and frontal lobe regions than their peers. In fact, this asynchrony was directly correlated with the inhibitory control performance in

emotional contexts from the fMRI task behavior and was specific to FHP adolescents, such that weaker synchrony was correlated with poorer cognitive control performance in these youth. The combined methodologies within the same participant sample indicate that (i) emotional information itself impacts frontal lobe functioning in FHP youth and (ii) the intrinsic synchrony of affective and cognitive networks may be aberrant in at-risk youth and, as a result, impact task-related brain response and performance. Thus, by using more than 1 imaging modality in the same group of participants, we may be better informed to answer questions about neural networks and behavior.

LIMITATIONS AND FUTURE DIRECTIONS

While this study presents novel findings in neurobiological markers of risk for alcoholism in FHP youth, there are some limitations that warrant mention. First, FHD of alcoholism only related to BOLD response in 1 region of the whole-brain fMRI analysis. While there are certainly specific genetic factors that have been associated with the transmission of familial alcoholism, the influence of environment could also contribute to risk. This may complicate the relationship between an FHD score and behavioral or brain measures. Second, surprisingly, no significant group differences were found between FHP and FHN youth in response to negative emotional faces. According to the exit questionnaire, scared and calm faces were interpreted with comparable valence and arousal, which could be explained by differences in brain response to neutral faces during adolescence (Thomas et al., 2001). While “calm” faces were used in this study to be more valid control stimuli, the lack of a subjective distinction between fearful and calm faces may have prevented the detection of significant group differences in brain response to this contrast. Third, comparison of inhibitory control brain response during emotion versus gender identification could be different in the level of difficulty, although there was no main effect of Emotion on target face accuracy or nogo commissions, and thus presumably no overall difference in task difficulty. Fourth, while previous studies have found behavioral deficits in emotional processing and executive functioning among FHP youth (Christensen and Bilenberg, 2000; Corral et al., 1999), the current study did not. Thus, it is uncertain whether behavioral differences would emerge in nonlaboratory settings where more demands are placed on emotional processing and cognitive control. Finally, as this study cannot point to cause-and-effect relationships, longitudinal investigations of FHP youth will be necessary to examine whether baseline abnormalities in affective and cognitive control circuitry will be predictive of future heavy alcohol use initiation.

CONCLUSIONS

To our knowledge, this is the first study to examine emotional and cognitive control circuitry and investigate the intrinsic functional connections of the amygdala with the rest of the brain in FHP youth in the absence of heavy alcohol use. Furthermore, the combination of task-based fMRI and rs-fcMRI in the same study was able to show behavioral correlates of resting state synchrony in at-risk youth. The findings of reduced brain activity to positive emotional stimuli, weaker executive functioning brain response within emotional contexts, and altered amygdalar functional connectivity in FHP youth provide potential new targets to inform prevention scientists working to reduce the incidence of AUDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

All participants completed the Emotional Go-NoGo task in the scanner. There were 4 runs of the task: 2 emotional runs (A and B) and 2 control runs (C and D). The presentation of emotional runs was counterbalanced across participants, but always followed the presentation of control runs. Participants were instructed to respond as quickly and as accurately to the target face that was specified for a particular run and not to respond when a nontarget face appeared. Each face was presented for 500 ms with a 2- to 12-second jitter used as the intertrial interval for the emotional runs of the task, and 2- to 11.5-second jitter used for the control runs of the task. A fixation cross appeared during the jitter period.

Fig. 2.

FHP youth show blunted brain response to happy versus calm faces in 2 clusters in the left superior temporal cortex compared with their peers. Multiple comparison corrected ($p/\alpha < 0.01/0.05$). Results are surface-mapped onto a Population-Average, Landmark-, and Surface-based (PALS-B12) template brain in Talairach space. FHN, family history negative; FHP, family history positive; $*p < 0.05$.

Fig. 3.

Compared with their peers, FHP youth have weaker cognitive control brain activity during both positively valenced (**A**) and negatively valenced (**B**) emotional contexts in frontal, dorsal striatal, and parietal regions, as well as in 1 cluster of the default mode network (parahippocampal gyrus). The pattern of activation for cluster 2 is comparable to the bar graphs represented for cluster 1, while the patterns of activation in clusters 4 to 7 are comparable to the pattern of activation represented in the bar graphs for cluster 3. Multiple comparison corrected ($p/\alpha < 0.01/0.05$). Results are surface-mapped onto a Population-

Average, Landmark-, and Surface-based (PALS-B12) template brain in Talairach space.
FHN, family history negative; FHP, family history positive. $*p < 0.05$.

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Fig. 4.

FHP youth have significant differences in left (**A**) and right (**B**) amygdalar resting state functional connectivity patterns compared with FHN youth. These regions were defined with peaks at least 10 mm apart and spheres with 10 mm radii. Brain activity maps with Z -2.25 indicate greater segregation or less integration in FHP youth compared with FHN youth, and Z 2.25 indicate greater integration or less segregation in FHP compared with FHN youth. Examples are bar graphed for the left amygdala to illustrate the patterns of connectivity for each group. Multiple comparison corrected ($p < 0.05$, $z = 2.25$, 53 contiguous voxels). Cortical results are surface-mapped onto a Population-Average, Landmark-, and Surface-based (PALS-B12) template brain, while cerebellar results are displayed on a template brain in volumetric (Talairach) space. BA, Brodmann area; CER, cerebellum; FHN, family history negative; FHP, family history positive; L, left; MFG, middle frontal gyrus; MTG, middle temporal gyrus; PC, precuneus; PG, postcentral gyrus; R, right; SFG, superior frontal gyrus.

Fig. 5.

FHP youth have a significant relationship between left amygdala and left superior frontal gyrus functional connectivity, such that reduced connectivity is associated with poorer performance (fewer correct rejections) on the Emotional Go-NoGo task ($r = 0.72$, $p = 0.0017$). However, this relationship is absent in FHN youth ($r = -0.13$, $p = 0.60$). FHN, family history negative; FHP, family history positive.

Table 1

Participant Demographics for Youth with Valid fMRI Data

	FHP	FHN	Statistic	<i>p</i> -Value
<i>N</i>	19	17		
Age	14.92 (1.34)	14.69 (1.10)	$t_{34} = 0.55$	0.58
Gender	10F/9M	7F/10M	$\chi^2_{1} = 0.47$	0.49
Caucasian (%)	89.47	82.35	$\chi^2_{1} = 0.38$	0.54
IQ ^a	110.84 (10.86)	113.29 (9.19)	$t_{34} = 0.73$	0.47
SES ^b	32.0 (11.49)	27.12 (13.70)	$t_{34} = 1.16$	0.25
Tanner stage	3.89 (1.10)	4.12 (0.70)	$U_{34} = 151.5$ $Z = 0.34$	0.75

FHN, family history negative; fMRI, functional magnetic resonance imaging; FHP, family history positive.

Means and standard deviations unless otherwise noted.

^aWechsler Abbreviate Scale of Intelligence.^bHollingshead Index of Social Position.

Table 2

Performance on the Emotional Go-NoGo Task

	FHP	FHN
<i>N</i>	19	17
Hits		
Happy	57.95 (2.74)	57.88 (3.77)
Scared	57.26 (3.62)	56.59 (3.69)
Calm	58 (1.83)	56.24 (3.56)
Correct rejections		
Happy	21.21 (3.29)	22.88 (3.14)
Scared	21.16 (3.98)	23.47 (2.32)
Calm	20.68 (2.85)	21.65 (2.74)
Reaction time (milliseconds)		
Happy	523.87 (74.62)	585.36 (109.2)
Scared	573.33 (109.5)	654.04 (160.16)
Calm	519.44 (79.54)	574.53 (167.78)
D-prime		
Happy	2.99 (0.83)	3.33 (0.63)
Scared	2.89 (0.92)	3.14 (0.63)
Calm	2.83 (0.62)	2.74 (0.76)

FHN, family history negative; FHP, family history positive.

Means and standard deviations unless otherwise noted.

Hits = out of 60 total possible hits for each emotional condition. Correct Rejections = out of 26 possible correct rejections for each emotional condition. D-Prime = higher values indicate greater signal detection.

Table 3

Between-Group Results for Go Contrasts and NoGo Contrasts in Different Emotional Contexts. Peak Location, Regions Included, Voxel Number, and Peak Talairach Coordinates Are Provided for Each Cluster

Peak anatomic location	Regions included	No. of voxels	x	y	z	t-Statistic	Cohen's d
FHP vs. FHN							
Go							
Happy > Calm							
None							
Happy < Calm							
L STG	L insula, L postcentral gyrus	40	-59	-26	15	-3.05	1.04
L STG		31	-56	8	-10	-3.20	1.10
Scared > Calm							
None							
Scared < Calm							
None							
Calm NoGo							
Happy > Calm							
None							
Happy < Calm							
R SFG	R MFG	111	20	50	45	-3.28	1.12
R SFG		18	29	68	3	-2.86	0.98
Scared > Calm							
None							
Scared < Calm							
R caudate	L caudate	43	2	2	12	-3.18	1.09
R SFG		32	20	50	45	-3.10	1.06
L MFG	L IFG	24	-47	41	18	-3.06	1.05
R PG		21	20	-20	-28	-3.16	1.08
L MFG		20	-38	35	42	-3.09	1.06
R IPL	R MTG	18	50	-68	33	-3.12	1.07
R SFG		18	2	29	48	-3.01	1.03

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FHN, family history negative; FHP, family history positive; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MTG, middle temporal gyrus; PG, parahippocampal gyrus; R, right; SFG, superior frontal gyrus; STG, superior temporal gyrus.

Table 4

Head Movement for Youth with Valid Resting State Functional Connectivity Data

	FHP	FHN	Statistic	<i>p</i>-Value
<i>N</i>	16	18		
Percentage frames removed	13.71 (11.11)	11.85 (9.78)	$t_{32} = 0.52$	0.61
Mean DVAR ^a remaining mean	5.93 (0.69)	6.06 (0.52)	$t_{32} = 0.64$	0.53
FD ^b remaining mean	0.11 (0.03)	0.12 (0.04)	$t_{32} = 0.53$	0.60

FHN, family history negative; FHP, family history positive. Means and standard deviations unless otherwise noted.

^aVariation in Normalized Signal Intensity.

^bFrame-to-Frame Displacement.

Table 5

Participant Demographics for Youth with Valid Resting State Functional Connectivity Data

	FHP	FHN	Statistic	<i>p</i> -Value
<i>N</i>	16	18		
Age	15.02 (1.31)	14.85 (1.19)	$t_{32} = 0.41$	0.68
Gender	8F/8M	7F/11M	$\chi^2_1 = 0.42$	0.52
Caucasian (%)	81.25	77.78	$\chi^2_1 = 0.06$	0.80
IQ ^a	112.31 (8.3)	111.78 (10.59)	$t_{32} = 0.16$	0.87
SES ^b	31.2 (13.13)	27.17 (13.45)	$t_{32} = 0.88$	0.39
Tanner stage	4.0 (1.21)	4.17 (0.71)	$U_{32} = 142.5$ $Z = 0.06$	0.96

FHN, family history negative; FHP, family history positive. Means and standard deviations unless otherwise noted.

^aWechsler Abbreviate Scale of Intelligence.

^bHollingshead Index of Social Position.

Significant Group Differences in Whole-Brain Amygdalar Resting State Functional Connectivity Between FHP and FHN Youth

Table 6

	FHP	FHN	No. of Voxels	Peak Talairach (x, y, z)	FHP		FHN		z-Statistic	Cohen's <i>d</i>
					SD	SD	Fisher's <i>z</i>	SD		
<i>N</i>	16	18								
L amygdala										
L SFG	-	+	58	-4, 29, 53	-0.08	0.04	0.003	0.05	-3.98	1.83
L precuneus	-	+	94	-5, -48, 34	-0.05	0.09	0.07	0.09	-3.44	1.86
L SFG/BA8	-	+	87	-20, 15, 42	-0.06	0.04	0.01	0.05	-3.44	1.58
L cerebellum	+	-	53	-20, -58, -45	-0.05	0.08	-0.05	0.07	-3.11	1.33
R cerebellum	-	+	54	21, -83, -34	-0.05	0.05	0.05	0.08	-3.57	1.46
R MFG	-	-	88	25, 12, 45	-0.10	0.04	-0.01	0.04	-3.81	1.95
R precentral gyrus	+	-	56	57, -9, 24	0.06	0.05	-0.04	0.06	4.04	1.86
R amygdala										
R cerebellum	+	-	56	30, -68, -18	-0.01	0.06	-0.06	0.05	3.27	1.48
R MFG	-	+	54	29, 8, 35	-0.07	0.06	0.03	0.06	-3.65	1.69
R MTG	-	+	54	45, -27, -8	-0.02	0.05	0.05	0.04	-3.37	1.58

+, positive functional connectivity; -, negative functional connectivity; BA, Brodmann area; FHN, family history negative; FHP, family history positive; L, left; MFG, middle frontal gyrus; MTG, middle temporal gyrus; R, right; SD, standard deviation; SFG, superior frontal gyrus.