EMOTIONAL PROCESSING AND BRAIN ACTIVITY IN YOUTH AT HIGH RISK FOR ALCOHOLISM

By

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ABBREVIATIONS

ACC – Anterior Cingulate Cortex
AFNI – Analysis of Functional NeuroImages
aI – Anterior Insula
AMYG – Amygdala
ANOVA – Analysis of Variance
ART – Affective Rating Task
ASPD – Antisocial Personality Disorder
AUD – Alcohol Use Disorder
BA – Brodmann Area
BDNF – Brain-Derived Neurotrophic Factor
BG – Basal Ganglia
BOLD – Blood Oxygen Level-Dependent
CDDR – Customary Drug Use and Drinking Record
CDI – Children's Depression Inventory
CG – Cingulate Gyrus
dACC – Dorsal Anterior Cingulate Cortex
DALYS – Disability-Adjusted-Life-Years
DLPFC – Dorsolateral Prefrontal Cortex
DMN – Default Mode Network
DPS – Diagnostic Interview for Children Predictive Scales
DSM-IV – Diagnostic Statistical Manual, Version 4
ERT – Emotion Recognition Task
FD – Frame-to-frame Displacement
FDR – False Discovery Rate
FG – Fusiform Gyrus
FIRST – Functional Magnetic Resonance Imaging of the Brain Integrated Registration and Segmentation Tool
FHD – Family History Density
FHP – Family History Positive
FHN – Family History Negative
FMRI – Functional Magnetic Resonance Imaging
FOV – Field of View
FWHM – Full Width at Half Maximum
FSL – Functional Magnetic Resonance Imaging of the Brain Software Library
GABA – Gamma-Amino Butyric Acid
GAD – Generalized Anxiety Disorder
HRF – Hemodynamic Response Function
IAPS – International Affective Picture System
ICU – Inventory of Callous-Unemotional Traits
IFG – Inferior Frontal Gyrus
IOG – Inferior Occipital Gyrus
IPL – Inferior Parietal Lobule
IQ – General Intelligence
L – Left
LG – Lingual Gyrus
MANOVA – Multivariate Analysis of Variance

MDD – Major Depressive Disorder
MeFG – Medial Frontal Gyrus
MFG – Middle Frontal Gyrus
MOG – Middle Occipital Gyrus
MRI – Magnetic Resonance Imaging
MTG – Middle Temporal Gyrus
NAcc – Nucleus Accumbens
OHSU – Oregon Health & Science University
OFC – Orbitofrontal Cortex
PFC – Prefrontal Cortex
PCC – Posterior Cingulate Cortex
PDS – Pubertal Development Scale
PG – Parahippocampal Gyrus
PSS – Perceived Stress Scale
R – Right
RMS – Root Mean Squared
ROI – Region of Interest
Rs-fcMRI – Resting State Functional Connectivity Magnetic Resonance Imaging
SAM – Self-Assessment Manikin
SES – Socioeconomic Status
SFG – Superior Frontal Gyrus
SHQ – Sleep Habits Questionnaire
SIMD – Substance Induced Mood Disorder
SMS – Tanner's Sexual Maturation Scale
SNR – Signal-to-Noise Ratio
SPL – Superior Parietal Lobule
STAI – Spielberger State-Trait Anxiety Inventory for Children
STG – Superior Temporal Gyrus
TE – Time to Echo
TG – Temporal Gyrus
TI – Inversion Time
TR – Repetition Time
UPPS-P-R-C – UPPS-P Impulsive Behavior Scale for Children
WASI – Wechsler Abbreviated Scale of Intelligence

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ABSTRACT

Individuals with alcohol use disorders (AUDs) have deficits in emotion recognition as well as atypical function and structure in brain regions important for affective processing. These symptoms are often associated with problems in executive functioning. Interestingly, even prior to heavy alcohol use, youth with a family history of alcoholism (FHP) are at greater risk for emotional problems and exhibit deficits in cognitive control compared to youth without a family history of alcoholism (FHN). Given that FHP youth are at much greater risk for developing an AUD than FHN youth, it is essential to clarify whether brain and behavior phenotypes related to the interplay between affective processing and executive functioning may be pre-morbid risk factors for the development of AUDs in FHP youth.

Thus, the goal of this study was to investigate brain function and behavior, related to emotional processing in FHP youth, as well as examine their associations with executive functioning, *prior to heavy alcohol use*. Specifically, this dissertation investigated emotional processing and its association with cognitive functioning using behavioral measures, which included an explicit emotion recognition task, as well as a subjective emotional valence and arousal rating task. Additionally, functional magnetic resonance imaging (fMRI) and resting state functional connectivity magnetic resonance imaging (rs-fcMRI) were used to examine brain response to emotional faces, cognitive control in emotional contexts, and the intrinsic connectivity between limbic and cortical brain regions.

The results of these studies suggest that FHP and FHN youth do not have significant differences in emotion recognition or subjective ratings of affective stimuli. However, fMRI showed that neural reactivity to emotional faces and cognitive control in emotional contexts were reduced in FHP youth compared to their peers, in left superior

temporal cortex, and fronto-striatal regions, respectively. These findings indicate blunted response to positively valenced faces and weaker cognitive control brain activity in FHP youth. Further, FHP youth had many differences from FHN adolescents in resting state synchrony between the amygdala, and other brain areas, including prefrontal cortex and cerebellum, suggesting that intrinsic brain connectivity may be altered in FHP youth. Specifically, weaker left amygdala to left superior frontal gyrus connectivity was related to more inhibitory control errors in FHP youth.

The findings from these studies present altered task-related and intrinsic brain response in limbic and cognitive control circuitry in FHP youth. This dissertation includes the examination of emotion recognition, affective ratings of emotional stimuli, brain response to emotional faces, emotion-cognition interactions, and resting state functional connectivity in FHP youth. By investigating brain activity and behavior in FHP and FHN youth prior to heavy alcohol use, these studies provides insight into the neural and behavioral phenotypes associated with familial alcoholism, which may relate to increased risk for developing AUDs. Understanding whether atypical emotional processing and associated deficits in cognitive control are present in FHP youth prior to heavy alcohol use will allow future research to establish prevention strategies aimed at reducing the development of AUDs.

CHAPTER 1. INTRODUCTION

1.1 Adolescent Alcohol Use: Prevalence, Risk, and Health-Related Consequences

Alcohol use dramatically increases during adolescence and continues to remain a major health burden to the individual and society. According to the World Health Organization, alcohol use is the leading contributor to global disability-adjusted-life-years (DALYs) between the ages of 10 to 24, accounting for approximately 7% of DALYs, which outnumbers other risk factors, such as unsafe sex or iron deficiency (Gore et al., 2011). Not only is adolescent alcohol use a burden to society as a whole, it has adverse consequences to the individual, including negative impacts on social, emotional, and academic functioning (Crosnoe et al., 2012), and is associated with greater risk for drinking-related accidents (Marcotte et al., 2012). Additionally, heavy drinking during adolescence increases the prevalence of other adverse behaviors, such as violence, unprotected sex, and other drug use (Miller et al., 2007). Despite declining rates of teenage alcohol use since the 1980's, alcohol is still the most widely used intoxicant among adolescents in the United States (Johnston et al., 2012). The 2011 National Youth Risk Behavior Survey administered to high school students indicated that while 70% of adolescents had ever used alcohol, approximately 20% started using before the age of 13 (Eaton et al., 2010). In fact, according to the 2011 Monitoring the Future Survey, 15% of 8th graders and >50% of surveyed 12th graders report having been drunk in their lifetimes (Johnston et al., 2012). Given the rates of use and the numerous associated negative outcomes, adolescent drinking represents a major public health concern.

One primary concern of adolescent alcohol use is its deleterious effects on adolescent brain development and behavior. Specifically, heavy alcohol use, such as

binge drinking, has been shown to have neurotoxic effects on the adolescent brain (Guerri and Pascual, 2010; Witt, 2010). Past month binge drinking, defined as the consumption of 5 or more drinks in an episode, was reported by nearly 22% of high school students (Eaton et al., 2010). With advanced neuroimaging technology over the last twenty years, we now know that alcohol abuse during adolescence results in atypical brain structure and functioning (for review, see (Jacobus and Tapert, 2013)). This is particularly concerning, given the ongoing maturation of the adolescent brain and the potential long-term consequences heavy alcohol use may have in later life and on subsequent functioning. Given the high rates of alcohol abuse during adolescence, work aimed at understanding specific risk factors that contribute to the emergence of heavy adolescent alcohol use is warranted. While several factors are associated with an increased risk of heavy drinking during adolescence, family history of alcohol dependence dramatically increases alcohol use disorder (AUD) risk (Cloninger et al., 1986; Goodwin, 1985; Schuckit et al., 1972). In the U.S., 25% of adolescents are estimated to have familial AUD (Grant, 2000), and offspring of alcoholics are 3-5 times more likely to develop an AUD than offspring of non-alcoholics (Cotton, 1979; Finn et al., 1990; Goodwin, 1985; Lieb et al., 2002; Merikangas et al., 1998; Schuckit et al., 1972). While the mechanisms by which AUDs are inherited are not fully understood and likely relate to co-morbid risk factors (Chassin et al., 1999; Malmberg et al., 2010; Martin et al., 2004; Rose et al., 2004; Schuckit, 1998), family history of AUD appears to be a robust predictor (Schuckit, 2000). Thus, understanding the behavioral and neural features of familial history risk is critical to identifying markers that may be associated with an increased risk for developing an AUD.

The aim of this dissertation is to identify pre-morbid characteristics related to emotional processing in youth with a family history of alcoholism (FHP) and examine

their associations with higher level cognitive functioning. While important steps have been taken to understand executive functioning in high-risk youth, the available evidence for emotional processing deficits in this population is lacking, despite shared abnormalities in affective neurocircuitry with alcoholics (Hill et al., 2001; Wrase et al., 2008). This reinforces the need to understand whether pre-morbid neurobehavioral traits related to emotional processing exist in high-risk youth that could lead to heavy alcohol use, or whether the observed affective deficits in alcoholics are primarily related to heavy drinking. Since both emotional and cognitive functioning systems are actively developing during adolescence, this dissertation is a novel contribution to current knowledge of neurobiological and behavioral traits associated with familial history risk for alcoholism during development. The long-term objective of this research is to contribute to the growing literature on brain and behavioral phenotypes that increase risk for developing an AUD, which will ultimately better inform prevention strategies aimed at reducing the incidence of adolescent onset alcohol abuse.

1.2 **Aims and Hypotheses of the Dissertation**

Based on previous research in alcoholics and FHP adolescents and adults, there were three aims for the current dissertation.

First, behavioral measures were administered to examine emotion recognition and subjective affective ratings in FHP and family history negative (FHN) youth. I hypothesized that FHP youth would have poorer recognition of negative emotional expressions, and reduced subjective arousal ratings of unpleasant affective images compared with their peers.

Second, functional magnetic resonanace imaging (fMRI) was used to investigate differences in brain activity to emotional facial expressions and the impact of emotional context on cognitive control behavior and brain activity. I hypothesized that FHP youth

would have blunted brain response to negative facial expressions compared with their peers, and that negative emotional context would result in poorer cognitive control behavior and reduce executive functioning-related brain activity in at-risk youth compared with FHN youth.

Third, resting state functional connectivity magnetic resonance imaging (rs-fcMRI) was used to examine intrinsic connectivity differences between the amygdala and executive functioning brain regions, including fronto-parietal, as well cingulo-opercular brain areas, between FHP and FHN youth, and this was correlated with task behavior. I hypothesized that FHP youth would have reduced intrinsic amygdalar functional connectivity with brain regions critical for executive functioning compared with their peers.

1.3 **Adolescence: A Critical Period of Brain Development**

Prior to a discussion of brain structure and function in youth at risk for alcoholism, it is important to understand normal, healthy adolescent brain development to provide a context for the aims of the current work. Adolescence is often defined as a transitional period between childhood and adulthood, which overlaps with the emergence of puberty, as well as changes in social relationships and psychological functioning. Structural brain imaging studies indicate that grey matter, composed mainly of neuronal cell bodies and dendrites, and white matter, which includes myelinated axonal fibers, undergo dramatic changes from childhood to adolescence and continue maturation into young adulthood (Bava et al., 2010; Casey et al., 2005; Giedd, 2004; Gogtay et al., 2004; Jernigan et al., 1991; Sowell et al., 2004). These studies show that overall grey matter volume peaks during early adolescence for both boys and girls. During this time of brain maturation, the process of synaptic pruning leads to the loss of unused synaptic connections, while synapses important for mature brain functioning are reinforced. This pattern of inverted

“U” grey matter development contrasts with the more linear growth of white matter volume (Giedd et al., 1999; Pfefferbaum et al., 1994) paralleled by increasing white matter integrity (Bava et al., 2010; Lebel et al., 2008), as measured through diffusion tensor imaging. Grey and white matter maturation has been linked to improvements in cognitive functioning during adolescence, including better working memory, visual, and language skills (Fryer et al., 2008; Klingberg, 2006). While many of these maturational changes lead to improvements in problem solving, decision-making, and inhibitory control during adolescence, this time also coincides with high risk for the emergence of psychopathology, including alcohol abuse (Andersen, 2003; Andersen and Teicher, 2008; Casey and Jones, 2010; Chambers et al., 2003; Ernst et al., 2009). Understanding the neurodevelopmental features of this critical maturational period can aid investigations of youth who may be more vulnerable to develop alcohol abuse than their peers, as a result of risk factors, such as familial alcoholism.

Studies of adolescent brain development indicate that grey matter maturation takes place at considerably different rates across brain regions (Galvan et al., 2006; Giedd, 2004; Sowell et al., 2002). Specifically, maturation of subcortical brain structures, including the amygdala, a key area of emotional processing, and the nucleus accumbens (NAcc), which responds to rewarding stimuli, associated with pleasure, occurs much earlier than the development of brain areas necessary for higher order cognitive control functions, including the prefrontal cortex (PFC) (Galvan et al., 2006; Yurgelun-Todd, 2007). This imbalance of grey matter pruning between affect/reward-associated brain structures and executive processing brain regions is believed to underlie the increased susceptibility of adolescents towards psychopathology. Higher incidence of depression and anxiety, as well as impulsive and risky behaviors, are

characteristic of this time period compared to childhood, including risky experimentation with alcohol, such as binge drinking (Eaton et al., 2010; Pharo et al., 2011).

Many models of neurodevelopment explaining these changes in adolescent personality and behavior have been put forth, of which the *triadic model* has been widely accepted. In this model, regulatory capacity of the PFC over reward-related processing regions that respond to appetitive, or highly salient stimuli associated with approach, is limited during adolescence compared to that seen in adulthood (Ernst and Fudge, 2009; Ernst et al., 2006). According to this theory, risk-taking during adolescence is due to increased ventral striatal activity and limited activation of avoidance behavior regulated by threat-related processing in the amygdala. However, since emotional processing is also believed to be most heightened during adolescence (Herba et al., 2006), some hypotheses suggest that perhaps different regions of the amygdala modulate affective-related processing in non-social and social contexts. This could explain mixed findings for the pattern of amygdalar response during adolescence. Currently, however, there is a lack of evidence for this dissociation in human studies (Ernst and Fudge, 2009; Ernst et al., 2009). It is also important to consider that these systems are complex and that multiple pathways to risk may exist during adolescence and young adulthood. For example, the reward deficiency hypothesis proposes that blunted NAcc and amygdalar activity to reward anticipation may lead to increased risk-seeking during adolescence (Bjork et al., 2004). Additionally, blunted amygdalar activity to social stimuli is also believed to underlie risk for psychopathology, including alcohol abuse (Glahn et al., 2007), depression (Thomas et al., 2001a), and callous-unemotional traits (Marsh et al., 2008). As the aims of this dissertation are to understand emotional processing systems and their interaction with prefrontal cortical regions that exert regulatory capacity over subcortical brain areas, I focus on the development of affective brain regions, including

the amygdala, and its association with the top-down regulatory brain regions, which are those important for higher-level executive functioning. Cognitive control has also been widely investigated in adolescent neurodevelopmental studies using both behavior and fMRI, which is also reviewed in this section. Furthermore, I discuss what is currently known about emotion-cognition interactions during adolescence, an important area of research that has implications for understanding the developmental dynamics between these systems.

1.3.1 *Emotional Processing*

Human neuroimaging studies have shown many brain regions engaged in response to emotional stimuli, including both subcortical and cortical brain areas (Fusar-Poli et al., 2009). Affective responses are often studied in response to emotional facial expressions. The amygdala, hippocampus, fusiform gyrus, superior temporal gyrus (STG), frontal lobes, and insula are responsive to emotional facial stimuli (Adolphs, 2002). Of these, the amygdala has been most well characterized for its role in emotional reactivity, both to negative and positively valenced faces (Yang et al., 2002). Interestingly, although development of cerebral cortical areas are mostly associated with reductions in grey matter volume across adolescence, the current evidence suggests that amygdalar volume slightly increases during early adolescence (Ostby et al., 2009), and plateaus over the course of development. FMRI studies have investigated blood oxygen level-dependent (BOLD) response to fearful facial expressions, and show elevated amygdalar and fusiform gyrus activity in adolescents compared with adults (Guyer et al., 2008; Monk et al., 2003). Pubertal development is also associated with more widespread areas of brain activity to both positive and negative facial expressions, such that by age 13, frontal lobe regions including the ventrolateral and ventromedial prefrontal cortices also respond to emotional faces, areas in which brain activity is

absent in late childhood (Moore et al., 2012). Moreover, behavioral studies suggest that on emotion recognition tasks, children can easily recognize happy faces, but negative emotions are more difficult to identify, with recognition of fear and disgust improving with age (Durand et al., 2007; Herba et al., 2006; Thomas et al., 2007). Thus, the maturation of affective circuitry is critical to the normal development of emotional processing abilities that underlie healthy social functioning during adolescence.

1.3.2 *Cognitive Control*

Concomitant decreases in grey matter volume and increases in white matter integrity during adolescence are believed to relate to many of the improvements in executive functioning seen during this period (Luna et al., 2004). However, the relatively slow rate of development of cognitive control systems, such as the PFC, compared with heightened emotional and reward processing during adolescence, results in a large imbalance of cortico-limbic maturation. This model has been used to explain the increased rates of risk-taking during adolescence, since affectively driven subcortical systems do not have a fully developed top-down braking mechanism (Ernst et al., 2006; Yurgelun-Todd, 2007). For example, response inhibition is poorer in adolescents than adults, but improves markedly during the course of brain development (Luna et al., 2001). This behavioral change is paralleled by decreases in self-reported impulsivity, indicative of improved cognitive control capacity, from early adolescence to young adulthood, while sensation seeking follows an inverted “U” across this period (Steinberg et al., 2008). Inhibitory control has been studied using paradigms such as the go/nogo task and stop signal reaction time task, both of which have been used in adolescents undergoing fMRI scans (Galvan et al., 2011; Hare et al., 2008; Heitzeg et al., 2010). Adolescents typically show decreased frontal, parietal, and striatal brain activity in these tasks compared with adults (Rubia et al., 2006). Over the course of adolescence, studies

report more focal and increased brain response of these areas during response inhibition, indicating more efficient utilization of these cortical systems during task performance (Tamm et al., 2002). Improvements in response inhibition and reaction time during this time reflect behavioral maturation of cognitive control that parallel the changes seen in brain response (Williams et al., 1999).

1.3.3 *Emotion-Cognition Interactions*

The interfering effect of emotional processing on cognitive control has received limited attention in behavioral and brain imaging studies of healthy adolescents. However, the examination of these systems in tasks that engage both subcortical and top-down circuitry is essential for a better understanding of the relationship between inhibitory control and affective processing. Developmental studies of children, adolescents, and adults have used a paradigm known as the emotional go/no-go task, a variant of the traditional go/no-go task, in which non-target stimuli are interspersed among target stimuli and response inhibition is required during their appearance (Hare et al., 2005; Hare et al., 2008; Somerville et al., 2011; Tottenham et al., 2011a). Emotional go/no-go tasks most often use emotional facial expressions as either target or non-target stimuli to examine both cognitive control and emotion regulation. Emotion regulation has been defined during conditions when non-target faces are emotional and target faces are neutral, while cognitive control occurs when the conditions are switched and non-target faces are neutral and go trials are emotional (Tottenham et al., 2011a). Using the latter strategy, it is possible to examine the effect of emotional interference on cognitive control in both positively and negatively valenced emotional contexts. Specifically, response inhibition during cognitive control conditions improves across development, when the preceding go trials are emotional faces (Tottenham et al., 2011a). Frontostriatal circuitry, including the inferior frontal gyus, anterior cingulate cortex (ACC),

and caudate, is associated with these improvements in cognitive control (Braver et al., 2001; Rubia et al., 2006; Somerville et al., 2011). However, some of the previous fMRI research has used block designs, precluding the dissociation of brain activity to specific trial types (Hare et al., 2005). Also, these studies either collapsed trial types (go and no-go) when analyzing brain response to emotional stimuli or did not compare brain activity during response inhibition based on the preceding emotional context of the target trials (Hare et al., 2008; Somerville et al., 2011). Additionally, none of these adolescent studies used control conditions in which both target and non-target stimuli were neutral (Wessa et al., 2007) to examine response inhibition during non-emotional contexts, compared with inhibitory control during different emotional contexts defined by the target emotional faces. These questions are addressed in the current dissertation to improve our understanding of emotion-cognition interactions in at-risk adolescents.

1.4 Alcohol Abuse and the Adolescent Brain

Since FHP youth are more likely to engage in early adolescent alcohol use (Dawson, 2000), they may be more prone to experience the neurotoxic effects of alcohol use during adolescence, which is associated with a variety of negative outcomes. Heavy alcohol use during adolescence is related to poorer neuropsychological functioning on many tasks, including those measuring response inhibition (Ferrett et al., 2011), working memory (Brown and Tapert, 2004; Brown et al., 2000; Squeglia et al., 2011), and decision-making (Johnson et al., 2008). Neuroimaging studies have shown that alcohol abusing teens have atypical grey matter volume in the PFC (De Bellis et al., 2005; Medina et al., 2008), and subcortical structures, such as the hippocampus (De Bellis et al., 2000; Nagel et al., 2005). Further, they have reduced integrity of white matter pathways, in both long-range connections between frontal and parietal brain regions as well as in pathways connecting subcortical and higher-order brain areas (Bava et al.,

2013; McQueeny et al., 2009).

FMRI studies have found reduced BOLD response in adolescent alcohol abusers in brain regions important for executive functioning during verbal and spatial working memory tasks (Squeglia et al., 2011; Tapert et al., 2004), and affective decision-making (Xiao et al., 2012). However, it is often unknown whether the above-mentioned deficits are a consequence of heavy alcohol use or if genetic and environmental factors, such as family history of alcoholism, may contribute to the brain activity patterns seen. The following section describes the importance of studying behavior and brain activity in familial alcoholism.

1.5 Risk Factor for Alcohol Use Disorders: Family History of Alcoholism

The observation that alcoholism runs in families has long been documented (Cotton, 1979; Goodwin, 1979; Schuckit et al., 1972). Over the past few decades, adoption (Bohman, 1978; Cloninger et al., 1981) and twin (Merikangas et al., 1998) studies have suggested that there is an increased likelihood of individuals with a family history of alcoholism to develop the disorder themselves (Cotton, 1979; Finn et al., 1990; Goodwin, 1985). These studies indicate that familial alcoholism is one of the most robust predictors of the development of an AUD during one's lifetime. Furthermore, this risk factor appears to be stable over time, since it also predicts the chronicity of alcohol dependence at multiple time points (Hasin et al., 2001). The intergenerational transmission of the disorder has been studied in families and cohorts with a high density of alcoholism, and indicates that higher familial density is often associated with greater risk (Hill and Yuan, 1999), with genetic vulnerability accounting for about 30-50% of individual risk (Heath et al., 1997; Kaprio et al., 1987; Knopik et al., 2004). FHP individuals without alcoholism are at high risk for poor health-related outcomes including hazardous alcohol use during adolescence (Lieb et al., 2002), college problem drinking

(LaBrie et al., 2009), psychiatric symptoms, including depression and anxiety (Chassin et al., 1999), as well as sleep abnormalities (Tarokh and Carskadon, 2010).

One of the best characterized findings in individuals with familial alcoholism are deficits in various domains of executive functioning (Hesselbrock et al., 1991), similar to what has been reported in alcoholics. For example, greater impulsivity and difficulties in response inhibition are seen in this population (Acheson et al., 2011a; Saunders et al., 2008), and FHP individuals are less able to delay reward gratification compared with their peers (Acheson et al., 2011b). FHP adults also have greater inhibitory problems when performing the Stroop, a color naming task that requires the maintenance of attention, conflict monitoring, and response inhibition. Individuals have to name the ink color of the words they see, despite the words themselves being names of colors, which causes conflict in naming the ink color. Additionally, during decision-making, FHP males are more attentive to financial gains, suggesting a greater propensity for reward-driven behavior (Lovallo et al., 2006). A study of various domains of executive functioning in non-alcoholic FHP and FHN adults, showed that individuals with familial alcoholism had greater preservative errors on the Wisconsin Card Sorting Task, and slower reaction time during the Trail Making and Arithmetic Switching Tasks, all of which are associated with set-shifting weaknesses (Gierski et al., 2013). These findings indicate that executive functioning difficulties are present in FHP adults who are not alcohol dependent and may be neurobiological markers associated with familial alcoholism.

While cognitive functions have been well characterized in FHP individuals, emotional processing and its relationship with executive control has received much less attention. Studies have found differences in emotional processing in FHP adults and their peers, including reductions in emotion-modulated startle (Miranda et al., 2002), blunted stress response (Sorocco et al., 2006), and higher rates of internalizing

symptoms (Sinha et al., 1989). Neuroimaging studies indicate smaller amygdala volume (Hill et al., 2001) and reduced brain activity to emotional images in FHP individuals (Glahn et al., 2007). Overall, these studies suggest that blunted emotional reactivity in FHP individuals may be a marker for their increased propensity to engage in risky behaviors, due to decreased threat-related response, but may also suggest socio-emotional deficits that could explain their susceptibility for heavy alcohol use. However, studies of FHP adults make it difficult to distinguish behavioral and neurobiological abnormalities that are associated with alcohol toxicity versus those that are specific to familial risk for alcoholism, as most participants have consumed substantial amounts of alcohol.

1.6 **Alcohol Use Disorders and Emotional Processing**

1.6.1 *Emotion Recognition and Affective Processing*

Research suggests that AUDs are associated with deficits in emotion recognition (Foisy et al., 2007b; Foisy et al., 2005; Philippot et al., 1999; Townshend and Duka, 2003), which may be related to atypical brain structure and functioning observed in the limbic system among alcoholics (Gilman and Hommer, 2008; Marinkovic et al., 2009; Salloum et al., 2007; Wrase et al., 2008). Alcoholics not only tend to overestimate the intensity of emotions seen in faces (Foisy et al., 2005; Philippot et al., 1999; Townshend and Duka, 2003), buy they also make more negative emotional attributions (Foisy et al., 2007b; Philippot et al., 1999), and often confuse one emotion for another, such as mislabeling disgust as anger or contempt (Philippot et al., 1999). Additionally, these deficits seem to be specific to alcoholism, since alcoholics, both recently abstinent and long-term abstinent, perform poorer on emotion recognition tasks than individuals with other drug abuse history (Kornreich et al., 2003). Alcoholics have also been shown to have slower reaction time when recognizing emotions (Foisy et al., 2007b; Maurage et

al., 2008), and when controlling for slowed reaction time on multiple identification tests (gender, age, race), the deficits remain specific to identification of emotional facial expressions (Maurage et al., 2008). Furthermore, poorer accuracy on emotion recognition tasks in alcoholics does not improve across the duration of the task, even though better performance is seen over time with other drug abusers (Kornreich et al., 2003). Recently, these emotion recognition difficulties have been extended to deficits of affect identification in emotion-word processing, music, voices, as well as complex interactions, suggesting a more severe deficit in socio-emotional functioning among alcohol abusing individuals (Amenta et al., 2013; Endres and Fein, 2012; Kornreich et al., 2013). In a discrete emotion recognition paradigm, similar to what is proposed in the current dissertation, polysubstance abusing adults, the majority of whom were alcohol abusers, showed emotion recognition deficits on angry, disgusted, fearful, and sad faces (Fernandez-Serrano et al., 2010). Based on the evidence of emotion recognition deficits in alcoholics, it is necessary to determine whether similar difficulties are present in FHP youth that could be disruptive to emotional functioning and may contribute to the ultimately higher prevalence of alcohol abuse in this population.

1.6.2 *Brain Structure and Function*

In addition to emotional processing deficits, alcoholics have various structural and functional abnormalities in affective processing brain regions. Studies of the limbic system have found reduced volume in subcortical structures, including the amygdala, thalamus, ventral striatum, and hippocampus among adult alcoholics (Durazzo et al., 2011; Makris et al., 2008; Wrase et al., 2008). Interestingly, amygdalar volume, specifically, has been related to craving and propensity to relapse, such that alcoholics with smaller amygdalar volumes, are more likely to continue drinking after six months of abstinence (Wrase et al., 2008). Relationships between abnormalities in brain structure

and performance on an emotional Stroop task have also been found in alcoholics. In particular, reduced integrity of cingulate and callosal fibers directly relates to Stroop-word interference in an emotional Stroop paradigm, in which emotional faces follow a color cue and precede a Stroop word (Schulte et al., 2011). This indicates that despite inaccurate recognition of emotional faces, alcoholics may still be vulnerable to emotional interference during cognitive control, and that these deficits have structural correlates in the brain.

In contrast to structural studies, functional studies of brain activity in alcoholics in response to emotional stimuli have been limited. Marinkovic et al. (2009) used an emotional face encoding task to examine brain response in alcoholics and controls to negative, positive, and neutral emotional expressions. Compared with controls, alcoholics exhibited both amygdalar and hippocampal hypoactivity during face encoding, and when recognizing deeply encoded faces, alcoholics had significantly reduced amygdalar activity to positive and negative emotional expressions compared with controls. These results help explain findings in behavioral studies of alcoholics that have found considerable evidence for emotion recognition deficits in this population. Furthermore, during an emotion identification paradigm, alcoholics showed comparable performance to controls, but had reduced brain response in the affective division of the ACC to disgust and sadness, with this lack of affective response to aversive stimuli believed to underlie disinhibitory traits in AUDs (Salloum et al., 2007).

There is also evidence to suggest that non-alcohol abusing FHP individuals share similar deficits in affective systems to alcohol abusers, including reduced amygdalar volume, less amygdalar activity in response to emotional stimuli, and high rates of internalizing symptoms (Benegal et al., 2007; Glahn et al., 2007; Hill et al., 2001; Marinkovic et al., 2009; Oscar-Berman and Bowirrat, 2005; Sinha et al., 1989; Wrase et

al., 2008). Furthermore, research examining the relationship between emotional processing and cognition has found that poor inhibition in individuals with co-morbid substance and alcohol abuse is associated with atypical arousal in response to affective images (Verdejo-Garcia et al., 2006), and affective measures in FHP alcoholics also relate to deficits in executive functioning (Sinha et al., 1989). This suggests that familial history of AUDs may put individuals at greater risk for problems with emotional processing (Oscar-Berman and Bowirrat, 2005; Sinha et al., 1989) and associated disruptions in executive functioning (Sinha et al., 1989), which could, in turn, increase risk for alcohol abuse (Fox et al., 2008; Labudda et al., 2010).

1.7 **Chicken or the Egg: Youth with a Family History of Alcoholism**

There are many advantages to studying behaviors, brain morphology, and brain activity in adolescents with familial alcoholism. Unlike their adult counterparts, youth with familial alcoholism can be selected to be free of heavy alcohol or substance use, precluding the effects of these substances on the observed measures of interest. Further, by studying youth prior to heavy alcohol use, characteristics associated with alcohol abuse risk can be identified during an active period of brain maturation, allowing the detection of risk markers during a period of brain development associated with increased vulnerability for alcohol abuse.

1.7.1 *Cognitive Control*

Both child and adolescent offspring of alcoholics have been studied with respect to performance on tasks of executive functioning (Corral et al., 2003; Corral et al., 1999; Harden and Pihl, 1995; Poon et al., 2000; Sher et al., 1991). Specifically, children with multigenerational familial alcoholism have poorer performance on neuropsychological measures of attention and visuospatial abilities (Corral et al., 1999; Poon et al., 2000). These children also have more perseverative errors on the Wisconsin Card Sorting Task

upon follow-up and do not meet performance levels of control youth (Corral et al., 2003), suggesting that executive control deficits are present in alcohol-naïve FHP youth. Poorer response inhibition in FHP adolescents indicates additional weaknesses in cognitive control among these youth (Nigg et al., 2004). Furthermore, adoption studies have provided evidence for a genetic component to disinhibitory traits observed in FHP youth. Specifically, the prevalence of alcohol and substance use, aggression, impulsivity, peer deviance, antisocial personality, and delinquent behavior, is greater in those adolescents with biological parents who have been diagnosed with an AUD (King et al., 2009). Other models have shown that paternal substance use disorder, in particular, predicts childhood neurobehavioral disinhibition, which in turn relates to adolescent substance use disorders 7-9 years later (Chapman et al., 2007). Thus, decreased cognitive control in FHP youth has been documented in both tasks of executive functioning and personality characteristics related to impulsivity.

Both structural and functional neuroimaging studies have provided increasing evidence that brain areas important for executive functioning are compromised in FHP youth. For example, FHP youth have increased cerebellar volumes (Hill et al., 2007b; Hill et al., 2011), as well as decreased laterality of orbitofrontal cortex (OFC) volume compared with FHN peers, which relates to allelic variation among different genes believed to underlie neuronal growth, including brain-derived neurotrophic factor (BDNF) and the alpha2 subunit of the gamma amino butyric acid (GABA) receptor (Hill et al., 2011). FMRI studies of executive functioning have consistently found reduced brain activity in FHP youth in the PFC and cerebellum, areas critical for cognitive control. Reductions in PFC BOLD response have been reported during a go-nogo task of response inhibition (Schweinsburg et al., 2004), suggesting that FHP youth do not activate areas needed for executive functioning to the same extent as their peers. During

verbal working memory, FHP adolescents show reduced PFC brain activity, even when controlling for reaction time differences between at-risk and control youth. These differences are largely due to significant variations between working memory and vigilance brain activity in FHN youth, while comparable brain response during the two conditions is seen in FHP youth (Cservenka et al., 2012). Similar findings are present in a spatial working memory task, in which FHN youth have increased PFC brain activity during spatial working memory and decreased PFC brain response during vigilance, while FHP youth show positive activation to both conditions (Mackiewicz Seghete et al., 2013). The overlap in findings from working memory studies suggest that these deficits may not be domain specific, but rather, reflect more widespread abnormalities in executive functioning brain response in at-risk adolescents. Furthermore, previous work in FHP youth indicated that despite comparable risk taking behavior, FHP adolescents show reduced risk taking related activity in the PFC and cerebellum, suggesting that during heated situations, these youth may not have the same resources for adaptive decision-making compared with their peers (Cservenka and Nagel, 2012).

1.7.2 *Affective Circuitry*

Although it is clear that adults with an AUD, as well as FHP adults, have abnormalities in the brain and behavior related to emotional processing, there is emerging research suggesting that similar deficits may be present in FHP adolescents, in the absence of alcohol abuse. Given the wealth of evidence for executive weaknesses both behaviorally and functionally in FHP youth, it makes sense to also examine characteristics related to emotional processing and their relationship with top-down cognitive control functions in these youth, since these systems are actively developing during adolescence (Giedd, 2004; Ostby et al., 2009; Somerville and Casey, 2010; Sowell et al., 1999; Sowell et al., 2002), and maturation of affective and appetitive

circuitry precedes that of higher order executive brain circuitry (Somerville et al., 2010; Van Leijenhorst et al., 2010; Van Leijenhorst et al., 2009; Yurgelun-Todd, 2007). FHP and FHN youth may differ in the development of appetitive and emotional brain systems and/or their respective functional relationships with later maturing executive processing brain regions, which could contribute to their increased risk for alcohol abuse.

Surprisingly, no studies of FHP youth have examined brain activity and behavior related to emotional processing and its relationship with executive functioning. **Figure 1** illustrates this circuitry, an adapted and modified diagram of the Papez-Maclean circuit (Iverson, 2000). This circuit was first described by Papez (Papez, 1937) to explain how emotional stimuli are processed in the brain, and was later modified by Maclean to include the amygdala and its relationship with the PFC (MacLean, 1949). Emotional stimuli may be processed quickly through a short path from the thalamus and its connectivity with the amygdala. A longer path to the amygdala involves the integration of sensory information from association cortices and the regulation of emotional processing through the cingulate gyrus (CG) connections to the amygdala. Importantly, higher order PFC regions, including dorsal ACC and DLPFC are responsible for cognitive control through connections to the CG. Emotional processing in the amygdala and its output through the hypothalamus may in return affect executive functioning.

Investigation of this circuitry in FHP youth is essential, since parental alcoholism is associated with emotional dysregulation and risk for affective problems in children (Christensen and Bilenberg, 2000; West and Prinz, 1987). Further, in adolescents, negative affect has been shown to mediate the relationship between parental history of alcoholism and risk-taking, the latter of which is significantly related to substance use (Ohannessian and Hesselbrock, 2008). Additionally, morphological studies in FHP youth, have found structural abnormalities in the OFC (Hill et al., 2009) and amygdala

(Hill et al., 2001), areas important for emotional processing that have reciprocal structural and functional connections with top-down executive control brain regions. More recently, 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). Additionally, Hill et al. (2007a) found that already drinking FHP adolescents and young adults may have socio-emotional deficits, since they show blunted brain activity during a theory of mind paradigm in areas implicated in social evaluation, including right middle temporal and left inferior frontal gyri. This provides further evidence for emotional deficits in at-risk youth, yet it is still unknown whether alcohol naïve FHP adolescents may show similar features in brain response to alcohol using FHP adults and alcoholics.

In summary, pre-morbid neural abnormalities in integrative affective and cognitive control circuitry may underlie the heritable aspects of AUDs. *To investigate these questions, the first aim of this dissertation used behavioral measures, including an emotional recognition task and an affective rating task to evaluate emotional processing in FHP youth. Based on previous research in alcoholics, I hypothesized that at-risk youth would have poorer emotion recognition skills when identifying negative facial expressions (sad, angry, scared, disgusted), but not positive facial expressions (happy and surprised). Furthermore, I anticipated that FHP youth would have lower arousal when rating affective pictures compared with their peers, given evidence for blunted emotional response in alcoholics and FHP individuals.*

The second aim of this dissertation examined neural reactivity to emotional faces and the impact of emotional context on cognitive control behavior and brain activity during an affective response inhibition task. I hypothesized that FHP youth would have blunted emotional reactivity to negative emotional expressions, and that response inhibition to non-emotional faces when target faces are negatively valenced would be

more difficult for FHP youth, as reflected by an increase in preservative errors. I also anticipated that in this condition, FHP adolescents would show reduced brain activity in dorsolateral prefrontal, inferior frontal, and anterior cingulate cortices, reflecting weaker cognitive control in the presence of a negative emotional context, compared with their peers.

1.7.3 *Resting State Functional Connectivity*

Finally, to better characterize the relationship between affective and cognitive control circuitry in youth at risk for alcoholism, the current dissertation employed rs-fcMRI to investigate the functional relationships between emotional and cognitive brain circuitry in the absence of task performance. Rs-fcMRI is a technique used to examine spontaneous fluctuations of BOLD activity in the brain when individuals are at rest in the scanner (Biswal et al., 1995). This method allows the designation of a seed region of interest (ROI) to examine the spontaneous correlations of BOLD response between that region and other areas of the brain. Areas that have positive spontaneous correlations with the seed region are believed to be "functionally connected" (Fox et al., 2005). Some of these brain regions, including medial prefrontal and posterior cingulate cortices, show deactivation during task-related fMRI, but greater activity during rest, and have been designated as part of the default mode network (DMN) (Greicius et al., 2003). In comparison, the fronto-parietal network includes a set of brain areas, such as the dorsolateral prefrontal cortex (DLPFC), and inferior parietal lobule (IPL), which show greater activation during cognitively demanding fMRI tasks, as they are necessary for moment-to-moment processing during executive functioning. Similarly, the cingulo-opercular network includes the anterior insula and dorsal anterior cingulate cortex (dACC), brain areas that represent "task-on" brain activation during set maintenance (Dosenbach et al., 2008; Dosenbach et al., 2007). Over the course of development, both

integration and segregation of brain regions are associated with typical maturational patterns of functional connectivity (Fair et al., 2007). For example, regions that form part of the DMN, including ventromedial PFC and posterior cingulate cortex (PCC), show stronger functional connectivity with age (integration) (Fair et al., 2008), while these regions also show greater segregation from other brain areas that form different networks, such as fronto-parietal regions. The separation of brain regions into distinct functional networks is also characterized by an increase of long-range connections during development, reflecting a more distributed, rather than local organization of brain architecture (Fair et al., 2007; Vogel et al., 2010).

While many cortical brain regions have been included in functional networks based on their patterns of activation during task-related fMRI and resting state, subcortical limbic regions, such as the amygdala, have not been assigned to any specific functional network. However, some studies are beginning to characterize the functional connectivity patterns of the amygdala in healthy populations, including children. For example, Qin et al. (2012) found that children have more immature integration (reduced positive connectivity) of the amygdala with other brain networks, including limbic structures (i.e. insula, hippocampus) and prefrontal cortical areas (ACC, inferior frontal gyrus (IFG), medial PFC, middle frontal gyrus (MFG)) compared with adults. This may indicate more local, as opposed to distributed, connectivity of this structure during childhood. However, an adult study of amygdalar resting state connectivity found that the amygdala is positively connected to other areas implicated in affective processing, including the OFC and the contralateral amygdala, while it shows negative functional connectivity (anti-correlated BOLD response) with areas implicated in higher-order cognition, such as regions of the fronto-parietal network (Roy et al., 2009). Thus, the examination of resting state synchrony of the amygdala with other brain regions is still in

its infancy, and further studies are needed to investigate typical and atypical connectivity of the amygdala across adolescence.

Recently, there have been studies of rs-fcMRI in alcohol abusers and abstinent alcoholics, which suggest various abnormalities in brain connectivity. For example, Chanraud et al. (2011) found weaker functional connectivity between the PCC, a main hub of the DMN, and the cerebellum in alcoholics. Other DMN abnormalities in alcoholics have been reported between limbic regions, such as the hippocampus and the cerebellum. Negative synchrony or segregation of these regions may be a result of neural compensation, since these individuals were matched to controls on performance during a face-name associative learning task (Pitel et al., 2012). Furthermore, reduced mammillothalamic resting state connectivity in chronic alcoholics has been shown to relate to poorer memory performance (Kim et al., 2009). Interestingly, short-term abstinent alcoholics also show weaker resting state synchrony in many different networks, including a reward network, defined by a NAcc seed, an emotion regulation network defined by a subgenual ACC seed, as well as networks defined by insular and visual cortex connectivity. Specifically, weaker functional connectivity within the emotional control network has been related to poorer performance on an affective go/no-go task in relapsers (Camchong et al., 2012).

A few recent studies suggest that there may also be evidence for pre-morbid functional connectivity abnormalities in FHP youth. While not a resting state study, our lab found weaker fronto-cerebellar connectivity in FHP youth when BOLD activity from various fMRI tasks was averaged (Herting et al., 2011). During an event-related working memory task, Wetherill et al. (2012) also found differences in fronto-parietal connectivity between substance-naïve FHP and FHN youth, despite similarities in task performance between the groups. While these studies suggest abnormalities in functional connectivity

in at-risk youth that could pre-date alcohol abuse, there have been no published studies to date of rs-fcMRI in FHP youth.

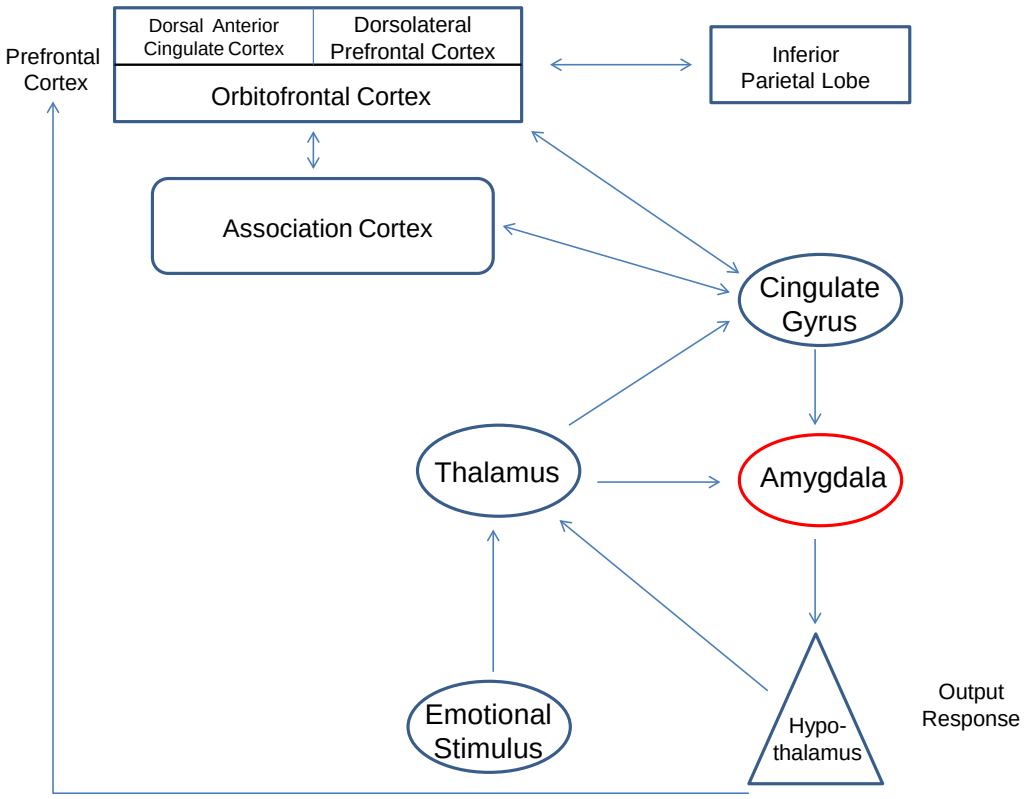
Thus, based on evidence of atypical limbic circuitry and connectivity in alcoholics, the third aim of this dissertation examined whether there are amygdalar rs-fcMRI differences between FHP and FHN youth, prior to heavy alcohol use. Specifically, the goal of this aim was to examine functional connectivity between the amygdala and pre-defined ROIs that are part of the fronto-parietal and cingulo-opercular network, which are important for top-down control. Right and left DLPFC, IPL, and dACC ROIs were selected for a priori analyses, based on previous evidence of atypical activity in these regions in FHP youth (Cservenka et al., 2012; Cservenka and Nagel, 2012; Schweinsburg et al., 2004; Silveri et al., 2011), as well as their critical roles in executive functioning (Rubia et al., 2006; Wagner et al., 2001). Given the evidence of both atypical executive control and limbic circuitry in alcoholics and FHP youth, I hypothesized that FHP youth would show reduced connectivity, indicative of immature synchrony between the amygdala and these a priori ROIs, including the DLPFC, IPL, and dACC.

1.8 **Summary**

Adolescent alcohol abuse is common and is associated with a greater incidence of lifetime AUD, as well as abnormalities in cognition, and brain structure and functioning (Brown et al., 2000; De Bellis et al., 2000; De Bellis et al., 2005; McQueeny et al., 2009; Medina et al., 2008; Nagel et al., 2005). Familial alcoholism, one of the strongest predictors of adolescent alcohol use (Cloninger et al., 1986; Goodwin, 1979; Schuckit, 1985), is associated with aberrant brain functioning and structure (Glahn et al., 2007; Heitzeg et al., 2010; Herting et al., 2011; Hill et al., 2001; Hill et al., 2007b; Schweinsburg et al., 2004; Silveri et al., 2011; Spadoni et al., 2008). Many abnormalities in emotional processing have been found in individuals with AUDs, as well as in FHP

adults (Foisy et al., 2007b; Foisy et al., 2005; Fox et al., 2008; Gilman and Hommer, 2008; Glahn et al., 2007; Marinkovic et al., 2009; Miranda et al., 2002; Oscar-Berman and Bowirrat, 2005; Philippot et al., 1999; Salloum et al., 2007; Sinha et al., 1989; Townshend and Duka, 2003; Uekermann et al., 2005); however, whether FHP adolescents exhibit atypical emotional processing and associated atypical emotional neurocircuitry, prior to heavy alcohol use, is currently unknown (**Figure 2**). In this dissertation, I used behavioral assessment, fMRI (**Figure 3A**), and rs-fcMRI (**Figure 3B**) to improve our understanding of these questions in an effort to inform future prevention strategies aimed at reducing alcohol abuse in high-risk youth. By increasing our knowledge of specific neurobehavioral phenotypes associated with family history of alcoholism risk, targeted efforts could be made towards offspring of alcoholics to provide them with educational and psychological resources designed to prevent heavy alcohol use experimentation during adolescence.

Figure 1. Emotional and Cognitive Control Circuitry of Interest in FHP Youth.



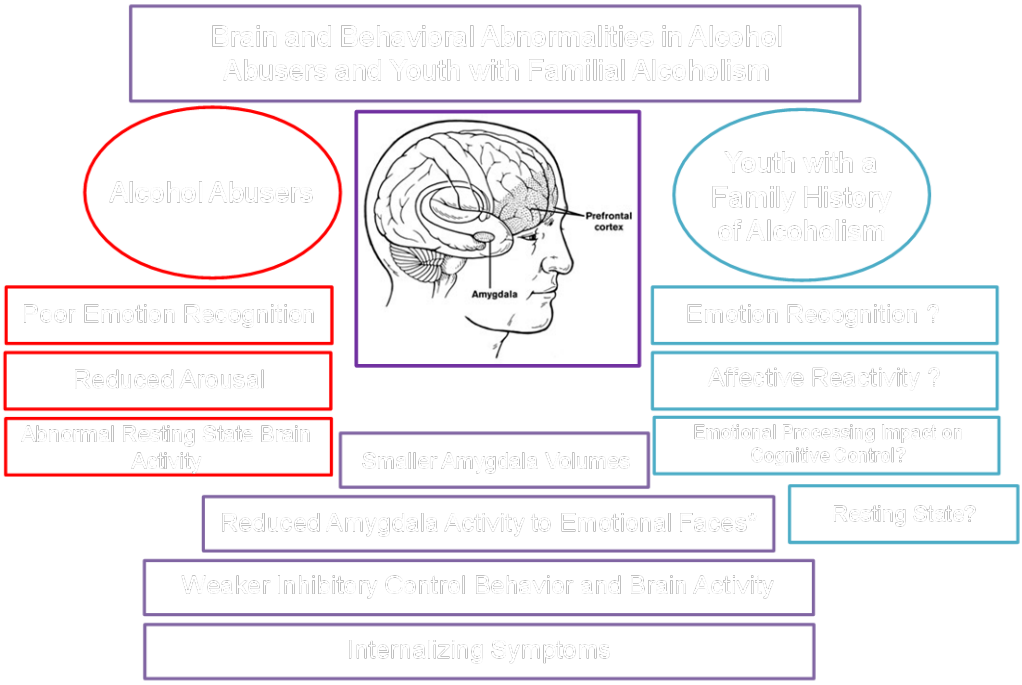
Adapted and modified from Iverson, Kupferman, & Kandel (2000)

This figure represents limbic and executive system connectivity as originally proposed by Papez and extended by Maclean to include the amygdala. Emotional stimuli are processed either by a direct route from the thalamus to the amygdala or through connections between the thalamus and the cingulate gyrus (CG), which receives input from higher order association cortices as well as the prefrontal cortex (PFC), further composed of dorsal and ventral regions. The CG integrates this information, and sends it to the amygdala. The output of the emotional information is sent through the hypothalamus, which has connections back to the PFC. The hippocampal pathway

originally included in the Papez circuit has been removed in this figure, as it is not central to the aims of this dissertation.

Within the PFC, the dorsal anterior cingulate cortex is responsible for conflict monitoring and top-down cognitive control. Dorsolateral PFC is implicated in many tasks of executive functioning and communicates with more ventral regions of the cortex, such as the orbitofrontal region, which has direct projections to the amygdala (not shown here). Importantly, higher-order executive functioning is also regulated by fronto-parietal connections (i.e. between the PFC and the inferior parietal lobule).

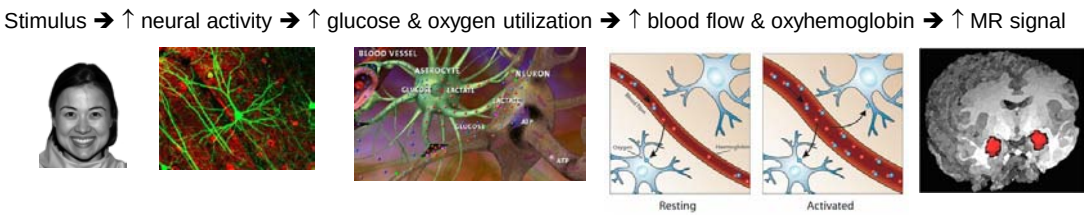
Figure 2. Atypical Brain and Behavioral Features Associated with Emotional Processing in Alcoholics and Youth with a Family History of Alcoholism.



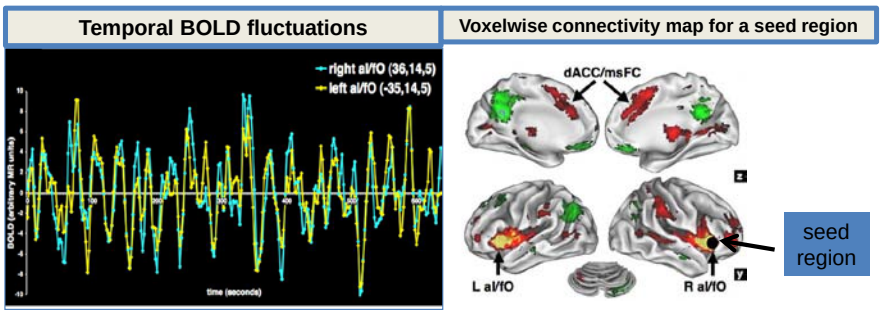
This figure illustrates shared deficits in emotional and cognitive processing in alcohol abusers and youth with familial alcoholism, outlined in purple boxes. Findings that are unique to alcohol abuse and emotional processing are outlined in red boxes, while questions that are explored in the current dissertation with respect to deficits that may pre-date alcoholism in family history positive youth are outlined in blue boxes. The cartoon brain in the center shows two major brain regions affected in alcoholism, the amygdala, which is necessary for affective processing, and the prefrontal cortex, the main brain area responsible for cognitive control. * = in alcohol abusers and FHP adults.

Figure 3. Brain Imaging Techniques.

A. Functional magnetic resonance imaging (fMRI)



B. Resting state functional connectivity magnetic resonance imaging (rs-fcMRI)



Adapted from Dosenbach, 2007

Figure 3A) Functional magnetic resonance imaging allows for the detection of blood oxygen level-dependent (BOLD) signal through a cascade of events that begin with neural activity in a specific brain region that is “activated” by a stimulus. Increased glucose and oxygen utilization in the brain region results in a large excess of blood flow to the brain area and an increase in oxygenated hemoglobin. A greater proportion of oxygenated, relative to deoxygenated hemoglobin allows for the detection of the BOLD signal.

Figure 3B) Resting state functional connectivity magnetic resonance imaging (rs-fcMRI) measures correlated BOLD signal fluctuations between a particular seed region and all other regions in the brain. Regions with activity that is significantly correlated with the seed region are considered “functionally connected”. This technique allows for the

examination of intrinsic connectivity of the brain at rest, independent of task performance. In this illustration, temporal BOLD fluctuations are significantly correlated between the left and right anterior insula (aI) and show positive functional connectivity with areas labeled in red, such as the dorsal anterior cingulate cortex (dACC). Anti-correlations, or negative correlations representing opposing patterns of BOLD fluctuations between two areas of the brain, are seen in brain regions labeled green. The seed region used to examine whole brain voxelwise functional connectivity was the right aI.

CHAPTER 2. MATERIAL AND METHODS

2.1 **Participant Recruitment and Exclusionary Criteria**

Adolescents 12-16 years old were recruited from the community using fliers, mailings, word-of-mouth, the university's research studies participation website, and local health fairs. A number of exclusionary criteria were used to determine study eligibility. Following a 15-minute telephone pre-screen with youth and parent, initial eligibility was determined. Youth assent and parent consent forms for minors were mailed to the families and reviewed over the phone. After signed assent and consent forms were received, a longer phone screen was scheduled. During that interview, the Diagnostic Interview for Children Predictive Scales (DPS) was administered to both parent and youth to exclude the presence of Diagnostic Statistical Manual-IV (DSM-IV) psychiatric disorders in youth (Chen et al., 2005; Lucas et al., 2001). Additionally, the Customary Drug Use and Drinking Record (CDDR) (Brown et al., 1998) was administered to youth to determine alcohol and drug use. 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/day, or any other drug use were automatically excluded. Additional exclusionary criteria for youth included: DSM-IV Axis I psychotic disorder in either biological parent (e.g. bipolar I or schizophrenia); prenatal exposure to alcohol or drugs; serious medical conditions; learning disability or mental retardation; inability of parent to provide family history; current use of psychotropic medications; premature birth (< 36 weeks); uncorrected vision problems; irremovable metal from the body, such as braces or a permanent retainer; left-handedness (Oldfield,

1971); and pregnancy. All procedures were approved by the Oregon Health & Science University (OHSU) Institutional Review Board.

2.2 **Participant Characterization**

2.2.1 *Family History of Alcoholism and other Psychiatric Disorders*

A modified version of the Family History Assessment Module (Rice et al., 1995) was used to characterize youth as FHP or FHN (Andreasen et al., 1977). One or both (when possible) biological parents of each participating youth were interviewed to assess the presence of AUDs in first and second degree relatives. Using interviews to assess family history information has been shown to be a useful and moderately reliable way of determining familial alcohol or substance use in a large group of relatives (Andreasen et al., 1986). Youth were classified as FHP if they had one or more biological parents with a past or present AUD or two or more second degree relatives (grandparent or aunts/uncles) on the same side of the family with an AUD. FHN youth had no history of alcoholism in either first or second degree relatives. Based on these criteria, 24 FHP and 22 FHN youth completed study visits.

Since previous research has suggested that family history density (FHD) may be related to symptomology (Stoltenberg et al., 1998), with higher density predictive of greater risk for alcoholism, a FHD score was calculated for each participant. This score was calculated for family history of AUD by assigning 0.5 to each biological parent with history of AUD, 0.25 for each grandparent with history of AUD, and a weighted score for each aunt or uncle with AUD, which was 0.25 divided by the total number of aunts/uncles on the maternal or paternal side of the family in which the AUD was reported.

Since other familial psychiatric disorders may be associated with atypical emotional processing in youth, we included questions assessing family history of other

DSM-IV psychiatric disorders, including major depressive disorder (MDD), generalized anxiety disorder (GAD), substance induced mood disorder (SIMD), and antisocial personality disorder (ASPD). The goal of assessing mood disorders in relatives was to understand whether the presence of these disorders differed by familial alcoholism status, since familial depression and anxiety disorders have also been associated with internalizing symptoms (Cents et al., 2011), atypical emotional processing, such as impairments in affective categorization (Mannie et al., 2007) and emotion-related brain activity (Mannie et al., 2008) in offspring. A similar score was calculated for a history of mood disorders in the family, in which the presence of MDD, GAD, or SIMD in a biological parent, grandparent, or aunt/uncle, resulted in the assignment of a FHD score for mood disorders. Multiple mood disorders in the same relative did not result in the assignment of multiple scores for that relative. The presence of mood disorders was summed across relatives for each youth, which resulted in the total family history of mood disorder density score for each participant. Finally, since internalizing symptoms have also been associated with familial ASPD (Coley et al., 2011), FHD of this disorder was calculated for youth using the same criteria outlined above.

2.2.2 *Puberty*

Puberty is characterized by the rise in gonadotropin releasing hormone signaling from the brain to the reproductive organs. This is associated with an elevation in sex steroid levels and results in reproductive capacity that is accompanied by the maturation of secondary sexual characteristics. Stage of pubertal development relates to brain development (Blanton et al., 2012; Giedd et al., 2006) and emotional processing (Goddings et al., 2012; Moore et al., 2012) during adolescence. Thus, to ensure that differences between FHP and FHN youth in this study were not related to pubertal stage, two measures were used to examine the developmental status of youth, with the intent

of covarying for any statistically significant group differences in subsequent analyses. Self-assessment of pubertal status was determined using the Pubertal Development Scale (PDS) (Petersen et al., 1988), and a modified line drawing version of the Tanner's Sexual Maturation Scale (SMS) (Taylor et al., 2001), which have been shown to have high concordance (Bond et al., 2006). The PDS is a five-item multiple-choice questionnaire asking youth about their developmental stage in growth, secondary sex characteristic maturation, such as increases in body hair, as well as skin changes associated with puberty. In addition, modified line drawings of the Tanner's SMS were used to collect self-reports on puberty. These drawings illustrate male and female development ranging from stage 1 (pre-adolescent) to stage 5 (adult-like maturation). Both mean PDS and Tanner's SMS scores are reported for each group.

2.2.3 *Socioeconomic Status*

Studies of socioeconomic status (SES) suggest that there are associations between parental SES and children's PFC brain activity (Hackman and Farah, 2009; Kishiyama et al., 2009; Sheridan et al., 2012). Furthermore, low SES is related to blunted affect (Silverman et al., 2009), and youth from high- and low-income families have differences in their stress response, as measured by salivary cortisol (Lupie et al., 2001; Sheridan et al., 2012). Given this evidence, it was important to examine whether FHP and FHN youth were comparable on SES, which was assessed using the Hollingshead Index of Social Position (Hollingshead, 1957). This questionnaire was administered to one of the youth's biological parents to determine education and occupational levels of both parents. Scores range from a scale of 1 to 7 for both education and occupation, with 1 indicating professional degree or professional occupation and 7 indicating less than seven years of education or unskilled worker. Occupation scores are multiplied by 7 and education scores are multiplied by 4 and then

added together to calculate the social position of the head of the household, defined as the parent who earns a higher income. In the event that the youth does not live with both parents, the head of the household is the parent who the youth spends most of his/her time with or the parent with the higher income when time is split equally between the two parents. Thus, scores may range from 11 to 77, reflecting upper to lower class categories.

2.2.4 *IQ*

There is some evidence that children of alcoholics and substance abusers have lower IQ than youth without such family history (Giancola et al., 1996; Ozkaragoz et al., 1997). To estimate general intelligence levels, the 2-subtest Wechsler Abbreviated Scale of Intelligence (WASI) was administered to all participants (Wechsler, 1999). The 2-subtest version of the WASI consists of Vocabulary and Matrix Reasoning sections. An estimated Full Scale IQ score was calculated for each youth.

2.2.5 *Perceived Stress Scale*

Since stress and emotional reactivity are closely associated during adolescence (Dahl and Gunnar, 2009), stress levels were examined in all youth by administering the Perceived Stress Scale (PSS) (Cohen et al., 1983). This 14-item paper-and-pencil questionnaire asks individuals to rate their level of stress in the last month. The questions ask how often individuals feel a certain way. Response options range from 1 = Never to 5 = Very Often. For example, one of the questions asks, “In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?” Half of the questions ask youth about their ability to positively handle stressors in the last month, and were thus reverse-scored (items 4, 5, 6, 7, 9, 10, 13). A total PSS score was calculated by summing the scores from the 14 items.

2.2.6 *Inventory of Callous-Unemotional Traits*

Previous research suggests that blunted affective response may be a risk factor for AUDs (Glahn et al., 2007) and has been reported in studies of alcoholics (Salloum et al., 2007). Thus, to further characterize affective processing differences between FHP and FHN youth, the Inventory of Callous-Unemotional Traits (ICU) was administered to all participants and one of their biological parents (Frick, 2004). This questionnaire has been previously validated in a large sample of 13-18 year old adolescents (Essau et al., 2006). Youth were administered the questionnaire during the neuropsychological assessment session, while parents completed the questionnaire while the youth was participating in the magnetic resonance imaging (MRI) scan. Statements on this 24-item measure are divided into three categories, including callous (items 2, 4, 7, 8, 9, 10, 11, 12, 18, 20, 21) uncaring (items 3, 5, 13, 15, 16, 17, 23, 24), and unemotional (items 1, 6, 14, 19, 22) traits. Response options to statements range from Not At All True (0) to Very True (3). Items 1, 3, 5, 8, 13, 14, 15, 16, 17, 19, 23, and 24 were reverse-scored. Scores are added together for each category, with higher scores reflecting greater callous/unemotional traits. A total ICU score was calculated for both the youth and parent questionnaire by summing the scores across the three categories. The relationship between youth and parent reports was examined by correlating the total score from each questionnaire.

2.2.7 *UPPS-P Impulsive Behavior Scale for Children*

Since previous studies have found differences in inhibitory control traits between FHP and FHN youth (Nigg et al., 2004), and different facets of impulsivity are associated with alcohol use in adolescents (Verdejo-Garcia et al., 2008), youth in the current study were administered the UPPS-P Impulsive Behavior Scale for Children (UPPS-P-R-C) (Zapolski et al., 2010), a revised version of the adult UPPS-P questionnaire (Whiteside and Lynam, 2001). The UPPS-P-R-C uses 5 subscales of impulsive personality

(negative urgency, lack of premeditation, sensation seeking, lack of perseverance, and positive urgency) to assess disinhibitory behaviors in youth, and has been validated in a large sample of elementary school children, in which it was shown to have good internal consistency and reliability (Gunn and Smith, 2010). The UPPS-P-R-C was also chosen because it allows for the dissociation of different types of impulsive personality, and subscales of this measure are related to drinking status in pre-adolescent children (Gunn and Smith, 2010). The questionnaire consists of 40 items, divided into 8 questions for each of the subscales. Participants are asked to choose the responses that best describe their personality on each of the items. The following rating scale was used for negative urgency (items 1, 7, 11, 17, 20, 26, 30, 32), lack of premeditation (items 4, 6, 10, 16, 23, 25, 28, 29), sensation seeking (items 2, 8, 12, 14, 18, 21, 27, 31), and lack of perseverance (items 3, 5, 9, 13, 15, 19, 22, 24): 1 – Agree Strongly, 2 – Agree Somewhat, 3 – Disagree Somewhat, 4 – Disagree Strongly. The rating scale: 1 – Very Much Like Me, 2 – Somewhat Like Me, 3 – Not Like Me, 4 – Not At All Like Me was used for the positive urgency items (33-40). All of the lack of perseverance and lack of premeditation items were reverse-scored, except for item 4. A mean score was then calculated for all items. For each of the subscales and the mean score, values closer to 1 reflect higher impulsivity and values closer to 4 reflect lower impulsivity.

2.2.8 *Children's Depression Inventory*

A measure of depression was collected on all youth to examine whether sub-clinical reports of depression may be related to emotion recognition or reactivity measures. The Children's Depression Inventory (CDI) (Kovacs, 1985) is a 27-item questionnaire assessing negative mood, ineffectiveness, anhedonia, negative self-esteem, and interpersonal problems. The questions ask participants to mark one of three statements that best describe how they have felt in the past two weeks. Scores of 0, 1,

or 2 are assigned for each item marked. Items 2, 5, 7, 8, 9, 10, 11, 13, 15, 16, 18, 21, 24, and 25 were reverse scored. Raw scores were converted to T-scores for each subscale, as well as the total T-score. Only the total T-score was examined in the current study. Despite no youth meeting DSM-IV criteria for depression using the DPS at the time of the phone interview screen, two FHN youth (1 male and 1 female) had T-scores ≥ 65 on the CDI at the time of assessment, suggesting clinical levels of depressive symptoms. These youth were excluded from all subsequent analyses of the dissertation.

2.2.9 *Spielberger State-Trait Anxiety Inventory for Children*

Prior to scanning, the state anxiety questions from the self-administered Spielberger State-Trait Anxiety Inventory for Children (STAI) (Spielberger et al., 1973) were completed by all youth in the study to assess situational anxiety. The questionnaire was administered to ensure low anxiety prior to the MRI scan session, as well as to examine whether pre-scan anxiety may have differed between FHP and FHN youth. This 20-item questionnaire consists of statements describing how the youth feels at that moment in time. Response options include 1 – Not At All, 2 – Somewhat, 3 – Moderately, and 4 – Very Much So. Items 1, 2, 5, 8, 10, 11, 15, 16, 19, and 20 were reverse scored. A total T-score was calculated for each participant. Lower T-scores reflect lower state anxiety.

2.2.10 *Sleep Habits Questionnaire*

A 25-item self-administered Sleep Habits Questionnaire (SHQ) was administered to all youth in the study to assess sleep quality and problems. This modified questionnaire incorporates items from the School Sleep Habits Survey (Wolfson and Carskadon, 1998). Children with sleep problems are at risk for early onset alcohol use (Wong et al., 2004), and those with a family history of alcoholism have atypical

electroencephalography patterns during sleep compared to their peers (Dahl et al., 2003; Tarokh and Carskadon, 2010). Also, sleep disturbances during adolescence have been associated with negative affect and poor inhibitory control (Moore et al., 2011). Thus, this questionnaire was used to examine whether comparable sleep habits were present between FHP and FHN youth. Specifically, total sleep time and scores were analyzed based on a composite of the Sleepiness and Sleep/Wake Problems Behavior scales. Responses to these items were summed, with lower summed scores reflecting fewer sleep problems.

2.3 **Data Reduction**

Since many demographic and personality measures were collected during the course of the study, variables were divided into two categories, including nuisance covariates and variables of interest. Nuisance covariates were dependent measures that were not related to the aims of the study, but that might lead to alternate explanations for observed aim-related group differences. These included age, pubertal measures, SES, and IQ. Variables of interest were those that measured personality or mood characteristics that may explain any potential differences on the main aims of the study. These included ICU-Youth and Parent questionnaires, PSS, CDI, and the UPPS-P-R-C. Additionally, FHD was a variable of interest in relation to both task-related performance and brain activity. Due to correlations among the personality/mood questionnaires of interest, ranging from r = 0.3-0.6, to avoid Type I error, multivariate analysis of variance (MANOVA) was used for examination of group effects on these variables.

2.4 **Multiple Comparison Correction**

To avoid Type I error that could arise from performing multiple statistical tests, analyses were corrected for multiple comparisons in the following manner. For main effects not central to the aims of the study (i.e. main effect of Emotion, rather than a

Group or Group x Emotion effect), Bonferroni correction was used for pairwise comparison of emotions in post-hoc tests. A more stringent method of correction was used because these post-hoc comparisons were not central to the hypotheses of the study, making it important to have a rigorous method of correction for unplanned comparisons. In instances that involved *a priori* hypotheses, such as ROIs in the resting state connectivity analyses (section 2.8.3) or variables of interest, such as correlations with FHD, the less stringent False Discovery Rate (FDR) correction was used, which in contrast to Bonferroni correction, only controls for the proportion of errors among the tests whose null hypotheses were rejected. Since it is more costly to have false negatives when correcting for multiple tests that involve hypotheses or variables of interest, a less stringent correction method was considered appropriate.

2.5 **Aim 1: Behavioral Assessment**

2.5.1 *Emotion Recognition Task*

To test discrete emotion recognition, participants performed a computerized Emotion Recognition Task (ERT) (**Figure 4**). During the task, participants were presented with 56 faces selected from the Pictures of Facial Affect dataset (Ekman and Friesen, 1976). This dataset is commonly used in adult (Fernandez-Serrano et al., 2010) and child/adolescent (Pajer et al., 2010; Singh et al., 1998) emotion recognition experiments, and includes 110 black and white photographs of facial emotional expressions of varying intensities. Each of the seven discrete emotions was selected for the task, including happy, sad, angry, fearful, disgusted, surprised, and neutral expressions. Faces were matched for gender, with eight faces being selected from each of the seven emotional categories. The task was programmed in E-Prime Version 1.1 (www.pstnet.com/eprime.cfm) by A.C. Presentation of emotional facial expressions was randomized. Each facial expression was presented on the screen for two seconds, and

the face then disappeared for two seconds, during which time responses were still recorded. Each emotion was associated with a button response on the keyboard, which remained consistent throughout the task (Happy – 1, Sad – 2, Angry – 3, Fearful – 4, Disgusted – 5, Surprised – 6, and Neutral – 7). These response options also appeared below the face presented, and remained on the screen until a two second interstimulus interval fixation period was presented prior to the next trial. Responses were recorded only if they occurred while the face appeared on the screen or during the two seconds that followed.

Participants were instructed by a trained research assistant on the task. The task instructions were to choose the correct response from the seven different options presented for each emotional face. Participants were told to use their right hand for responses and to respond as quickly as possible. They were told that responses could be made as soon as they saw the face was on the screen, and they did not have to wait for the face to disappear to make their response. A practice run was conducted on the computer to familiarize participants with the task, the speed of response needed, and the numerical keys assigned to each emotion. During practice, participants were presented with 14 emotional faces, 2 from each emotional expression, matched for gender. Following the practice run, participants performed the actual task. The total task time including practice, was approximately 7:00 minutes. The dependent variables on the task were the accuracy of emotion identification for each facial expression and the reaction time on each correct response.

2.5.2 *Affective Rating Task*

Participants' emotional processing of affective images was examined using pictures selected from the International Affective Picture System (IAPS) (Lang et al., 2008). Pictures from this dataset have been validated for use and appropriateness with

children and adolescents (McManis et al., 2001). When a previously validated picture was not present in the downloaded dataset, a picture of equal valence and arousal replaced the missing photograph. All pictures in this dataset are categorized as pleasant, unpleasant, or neutral. Categorization is based on the valence and arousal ratings of the pictures. The valence of a picture is determined by its level of happiness ratings on a Likert scale, while arousal is determined by the level of physiological response associated with viewing the picture, also rated on a Likert scale. Forty-five pictures were selected from the IAPS, fifteen from each emotional category. Participants performed a computerized Affective Rating Task (ART) programmed in E-Prime Version 1.1 (www.pstnet.com/eprime.cfm) by A.C (**Figure 5**). During the task, each picture appeared on the screen for six seconds, before disappearing, but participants had as long as they needed to make their button responses before a two second interstimulus interval was presented with a fixation cross, signaling the initiation of the following trial. Rating was performed on a nine-point Likert scale for valence, in which “1” was associated with unhappy, and “9” was associated with happy. As soon as a response for valence was made, participants were asked to rate their arousal when viewing the picture, also on a Likert scale, in which “1” was associated with bored/calm, and “9” was associated with excited/nervous. The self-assessment manikin (SAM) was used to aid participants with their responses (Lang, 1980). SAM is a cartoon figure illustrating the emotions one might identify with when viewing a picture, with the intensity of SAM’s expression varying on the 1-9 Likert scale.

Participants were instructed by a trained research assistant on the task. The task instructions were to focus on each picture when it appeared on the screen and rate on a scale of 1-9 using the keyboard, how unhappy or happy the picture made the participants feel. A response was followed by asking the participants on a scale of 1-9

how bored/calm or excited/nervous the picture made them feel. Participants were presented with three practice trials, before the actual task. The total task length varied depending on the reaction times of participants' responses, but on average, lasted just less than 10 minutes. The dependent variables from this task were valence and arousal ratings for pleasant, unpleasant, and neutral pictures.

To verify that participants were not distressed by viewing the emotional pictures, a brief paper-and-pencil questionnaire was administered following the task, which asked participants their overall valence and arousal on the same Likert scale. In addition, participants were asked if any of the pictures made them too scared, and if so, they could indicate which ones. Following completion of the questionnaire, the research assistant discussed the participants' responses with them to confirm that they did not leave the testing session feeling distress.

2.5.3 *Data Analyses*

In each group, dependent variables were inspected for normality. First, the Shapiro-Wilk test was used to examine statistically significant deviations from normality ($p < 0.05$). Any dependent variable that was significantly non-normal using this test was further examined with kurtosis and skewness calculations. Dependent variables with kurtosis or skewness values less than or greater than twice the standard error of skewness or kurtosis were transformed using square root or log transformations, as recommended by Tabachnick and Fidell (2007). In the event that transformations did not improve normality, non-parametric tests were used in data analyses. Nuisance covariates were compared between groups with independent samples *t*-tests or Mann-Whitney U-tests, when appropriate (see section 2.3 above). Chi-square tests were used to compare the groups on gender and race. Since analysis of variance (ANOVA) is considered to be robust to violations of normality (Glass et al., 1972), a 2x7 mixed model

ANOVA was used to examine emotion recognition accuracy and reaction time on the ERT, in which family history status was the between-subjects factor, and emotional facial expression was the within-subjects factor. 2x3 mixed model ANOVAs were used to examine affective ratings of valence and arousal on the ART. FHD scores were examined using bivariate correlations for their relationship with ERT accuracy and reaction time, as well as ART valence and arousal ratings for pleasant, unpleasant, and neutral stimuli. All statistical analyses were carried out in IBM SPSS Statistics version 20.0, while bar graphs and plots were created in GraphPad Software version 5.04 for Windows, GraphPad Software, La Jolla, California, USA, www.graphpad.com.

2.6 Participant Preparation for Magnetic Resonance Imaging Visit

All youth were scheduled for MRI visits within three months of the date of their screen, except on occasions when youth were unavailable for visits within that time period. In those cases, youth were re-screened prior to their participation in the study, to ensure that they were still eligible. Boys were scheduled at any time, while girls were scheduled for their visits during the follicular phase (within the first 10 days of their periods if they had menstrual cycles). This procedure was chosen because phase of the menstrual cycle has been shown to affect cognitive and emotional brain response during fMRI (Amin et al., 2006; Dietrich et al., 2001), and males and females show the most comparable performance on cognitive tasks when female estrogen (and progesterone) levels are low (Hampson, 1990). All but 2 FHN and 1 FHP girl(s) never had a menstrual period at the time of study participation. At the start of the MRI visit, parents filled out an MRI safety screening questionnaire on behalf of the participating youth, and all of these questions were reviewed with the youth prior to scanning. Girls were asked confidentially to confirm that there could be no chance they were pregnant at the time of the visit. Youth were then asked to complete the PDS and STAI questionnaires. In addition, they

were administered the Timeline Follow-Back measure (Sobell and Sobell, 1992) to ensure they had not used any alcohol or substances during the past 30 days that would make them ineligible for the study as well as to confirm no self-reported acute intoxication from alcohol or substances at the time of the visit. Participants then practiced the Emotional Go-NoGo task (section 2.7.1) on a laptop computer to familiarize themselves with the task prior to entering the scanner. A trained research assistant and scan operator (A.C.) explained the MRI procedures. Youth were given earplugs and MRI compatible headphones for the scan. Pillows were used for padding around participants' heads to limit head movement. A four-button MRI compatible optical button box was used for task responding. Youth were able to view the tasks during the scan through a mirror in the bore of the magnet that reflected the projection screen at the back of the bore.

2.7 **Aim 2: Functional Magnetic Resonance Imaging**

2.7.1 *Emotional Go-NoGo Task Stimuli and Procedures*

Participants completed a modified version of the previously published Emotional Go-NoGo task (**Figure 6**) (Hare et al., 2005; Hare et al., 2008) programmed in E-Prime Version 1.1 software (www.pstnet.com/eprime.cfm) by A.C. Four runs were performed in the scanner with happy, scared, or calm target faces and calm non-target faces. Only calm non-target faces were selected for nogo trials, because this study was aimed at examining cognitive control during emotional (happy or scared go faces) and non-emotional (calm go 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., 2001b).

Stimuli for the task were gray-scaled facial expressions selected from the NimStim facial pictures dataset (www.macbrain.org), which has been previously

validated (Tottenham et al., 2009), and published in studies of child and adolescent emotional processing (Han et al., 2012; Hare et al., 2008; Tottenham et al., 2011b). Stimuli were matched for gender and the number of appearances for each individual actor's facial expression. A total of 36 different faces were shown during the course of the four runs of the task, 12 happy, 12 scared, and 12 calm. The ratio of go to nogo stimuli was 70% go and 30% nogo faces for each run of the task (Somerville et al., 2011). Two runs with happy or scared go stimuli consisted of 60 emotional go faces and 26 nogo faces. Two other runs included male calm target faces in one run and female calm target faces in another run, each of which had 30 go and 13 nogo trials. The runs in which only calm stimuli were shown were later concatenated, resulting in 60 calm go trials, and 26 calm nogo trials. All stimuli were presented for 500 ms, with interstimulus intervals jittered between 2000 ms – 12000 ms, as determined optimal by Freesurfer's (Fischl, 2012) OptSeq (http://surfer.nmr.mgh.harvard.edu/optseq/), an fMRI experiment timing and optimization tool. Faces were presented pseudorandomly with the criteria that no more than three nogo faces would be presented in succession. The runs with emotional go and calm nogo faces lasted 8:00 minutes each, while the runs with only calm faces, divided by target gender, lasted 4:00 minutes each.

Participants were instructed to respond as quickly and as accurately as possible, and to only respond to the target face (happy, scared, male, or female) in a particular run. Before entering the scanner, all participants were familiarized with the instructions for the task and also completed a practice run on a laptop, in which a short HappyGo/CalmNoGo run was practiced as an example, but all run types were described to the youth by a scan assistant. In the scanner, task order was randomized across participants for the presentation of the emotional runs, such that half the participants

received the HappyGo/CalmNoGo run first, while the other half received the ScaredGo/CalmNoGo run first.

2.7.2 *Emotional Go-NoGo Exit Questionnaire*

Following completion of the fMRI tasks in the scanner, participants performed a computerized task, programmed in E-Prime Version 1.1 software (www.pstnet.com/eprime.cfm) by A.C., in which they were asked to rate the valence and arousal of the 36 faces they had seen during the Emotional Go-NoGo task in the scanner. Both valence and arousal were rated on a scale of 1-9, ranging from unhappy to happy for valence, and bored/calm to excited/nervous for arousal. Faces appeared randomly during the task, as well as across all participants. After a face appeared on the screen, participants had as long as they needed to respond first on valence, followed by arousal. The SAM (Lang, 1980) was used as a visual representation of valence and arousal to aid youth in their ratings when presented with a Likert scale. SAM appeared below each of the faces on the computer screen during each trial. Youth completed the task in approximately 5:00 minutes. Participants also completed a multiple-choice paper-and-pencil questionnaire, which asked them to answer questions on task motivation, difficulty, their perception of their own task performance, and reactivity to the emotional faces while in the scanner.

2.7.3 *Behavioral Data Analyses*

Participants who completed all four runs of the Emotional Go-NoGo task and met the performance criteria (≥ 14 correct rejections on nogo trials during the presentation of either Happy, Scared, or Calm target faces) to have sufficient data for modeling the hemodynamic response function (HRF) were included in the behavioral data analyses, resulting in 19 FHP and 17 FHN youth. The criteria used to examine normal distribution of task performance are consistent with the inspection of dependent variables described

in section 2.3.3. Emotional Go-NoGo task behavioral data was analyzed using a mixed model MANOVA, with reaction time, hits (correct identification of target faces), correct rejections (withheld responses on non-target faces), and d-prime (a measure of signal detection) as within-subjects measures, and family history status, as the between-groups variable. Valence and arousal responses from the exit questionnaire were examined with mixed model ANOVAs with happy, scared, and calm faces as within-subjects factors and family history status as the between-subjects variable.

2.7.4 *Image Acquisition*

Magnetic resonance imaging 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 tasks, a T1-weighted anatomical magnetization-prepared rapid acquisition with gradient echo sequence was acquired for co-registration of functional data to each participant's brain anatomy (Time Repetition (TR) = 2300 ms, Time to Echo (TE) = 3.58 ms, Inversion Time (TI) = 900 ms, flip angle = 10°, resolution = 1 x 1 x 1.1 mm, field of view (FOV) = 240 x 256 mm, 160 TRs, time of acquisition = 9:14). Echo planar imaging was used to collect fMRI data during four runs of the Emotional Go-NoGo task (TR = 2000 ms, TE = 30 ms, flip angle = 90°, resolution = 3.75 x 3.75 x 3.8 mm, FOV = 240 mm^2, 33 slices). Runs with emotional go and calm nogo trials included 237 TRs, lasting approximately 8:00 minutes each, while runs with only calm target (go) and distractor (nogo) faces, included 119 TRs, lasting approximately 4:00 minutes each. Total time for task acquisition was ~24 minutes.

2.7.5 *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. Motion correction was performed by finding the TR requiring the least amount of translational and rotational adjustment to align TRs to in each of the four runs (Cox and Jesmanowicz, 1999). Movement greater than 2.5 mm or 2.5 degrees in any of the translational or rotational directions was censored prior to further analyses. Further characterization of movement was done by calculating average root mean square (RMS) across the four runs of the task for each participant. Only participants with RMS < 1.5 mm were considered for the analyses. Functional data were blurred with a 6 mm full-width half maximum (FWHM) Gaussian filter and signal normalization was performed. Then, using AFNI's 3dREMLfit, a general linear model was used to estimate the BOLD response model for each regressor of interest (HappyGo, ScaredGo, CalmGo, Happy(NoGo), Scared(NoGo), and Calm(NoGo)) on correct go and correctly inhibited nogo trials. Misses on go trials (omission of response to target stimuli) and false alarms on nogo trials (commission of response when it needed to be withheld) were included as regressors of no interest, along with the six translational and rotational motion parameters. A one parameter gamma-variate function was used to model each regressor of interest, since this has been advised for stimuli lasting less than one second. Stimulus onset-times were entered for each of the regressors of interest to be convolved with the gamma-variate function and model the hemodynamic response for each individual subject. After individual-subject HRFs were modeled, functional data was resampled into 3 mm^3 voxels and transformed to standardized Talairach space (Talairach and Tournoux, 1988).

2.7.6 *Image Analyses*

Following the preprocessing steps for individual subject data, group analyses were performed to compare whole-brain activity for FHP and FHN youth on the contrasts

of interest. A total of 19 FHP and 17 FHN adolescents were included in this analysis, based on the minimum 14 of 26 (> 53%) correct rejections during each of the task conditions. As this study was interested in both differences in affective processing and cognitive control during different emotional contexts, the contrasts examined for the group-level analyses included HappyGo vs. CalmGo, ScaredGo vs. CalmGo, Happy(NoGo) vs. Calm(NoGo), and Scared(NoGo) vs. Calm(NoGo). To illustrate task-related activity in each group, one-sample *t*-tests were performed for each contrast in each group. To correct for multiple comparisons, AFNI's AlphaSim Monte Carlo simulation was used to determine the minimum cluster size needed at a voxel value of $p < 0.05$ and alpha value $\alpha < 0.05$ (number of voxels ≥ 205). (Forman et al., 1995). Next, for the between-groups analysis, individual group maps for FHP and FHN that were initially voxel thresholded at $p < 0.05$, were added together to comprise the task-related activity map. Thus, examination of group differences in brain response was confined to this predefined mask of task-related activity. Independent samples *t*-tests were used to compare groups on brain response in these contrasts. To correct for multiple comparisons, AFNI's AlphaSim Monte Carlo simulation was used to determine the minimum cluster size needed at a voxel value of $p < 0.01$ and alpha value $\alpha < 0.05$ (Forman et al., 1995). All contrasts of interest reported are multiple comparison corrected ($p/\alpha < 0.01/0.05$).

In addition to the whole-brain fMRI analysis, an ROI analysis was performed on the left and right amygdala to examine differences in neural reactivity to positively or negatively valenced faces between FHP and FHN youth. FMRIB Software Library (FSL)'s FMRIB Integrated Registration and Segmentation Tool (FIRST), an automated segmentation algorithm that uses grey and white matter boundaries to define subcortical nuclei in the brain (Patenaude et al., 2011), was used to delineate each participant's left

and right amygdala. For the ROI analyses, a less stringent voxel/cluster correction was used than for the whole-brain analyses. A minimum voxel and cluster correction of $p/\alpha < 0.05$ was applied, which required ≥ 16 contiguous voxels to be significant for the left amygdalar ROI and ≥ 15 contiguous voxels for the right amygdalar ROI.

2.8 **Aim 3: Resting State Functional Connectivity Magnetic Resonance Imaging**

2.8.1 *Image Acquisition*

Resting state data was acquired over two runs (TR = 2500 ms, TE = 30 ms, flip angle = 90°, resolution = 3.75 x 3.75 x 3.8 mm, FOV = 240 mm^2, 36 slices, 100 TRs, time of acquisition for each run: 4:17). While there are various ways to collect resting state data, including eyes closed, eyes open, or eyes open and fixating, participants in the current study were instructed to lie still and fixate on a white cross-hair in the middle of a black screen. This method was chosen as it has been shown to best characterize the resting state networks (Yan et al., 2009).

2.8.2 *Image Preprocessing*

Resting state data were preprocessed according to common procedures (Costa Dias et al., 2013; Fair et al., 2009; Fair et al., 2007; Mills et al., 2012) used to reduce spurious noise unlikely due to neuronal activity that may cause artifact and affect the spontaneous BOLD fluctuations of interest. These steps included slice timing correction due to interleaved acquisition, removal of a central spike due to MR signal offset, and signal normalization to a mode value of 1000. All anatomical images were transformed into 3 mm^3 voxels in standardized Talairach space (Talairach and Tournoux, 1988) and functional data was co-registered and transformed to the same atlas space. Co-registration of functional and anatomical data was visually inspected for each participant by A.C. to ensure proper alignment. Further connectivity preprocessing steps included a) a temporal band-pass filter to remove high frequency noise that may be due to heart rate

or respiration (0.009 Hz < f < 0.08 Hz), b) rigid body head motion correction by regression of the 3 translational and 3 rotational parameters, c) regression of the white matter and ventricular signal from pre-defined ROIs, d) regression of the global signal from the whole brain, and e) regression of the derivates of the white matter, ventricular, and whole-brain signals.

Since rs-fcMRI has been shown to be particularly sensitive to even small amounts of head movement, additional steps were taken to ensure that only participants with minimal head movement were included in the analyses and that FHP and FHN youth did not differ in amount of head movement. To ensure that TRs in which head movement may have affected the MR signal were excluded, TRs that had signal intensities with absolute values greater than 8, as measured by the variance of the signal change from the average signal (DVAR) were excluded (Shannon et al., 2011). The percentage of frames removed based on this algorithm was then calculated and a threshold of 40% was set, such that participants with greater than 40% of frames removed (80 out of 200 TRs), were excluded from further analyses. This threshold was chosen to ensure that all participants had a minimum of 120 TRs, or approximately 5 minutes of resting state data for functional connectivity analyses. Simulations show that this length of data collection is sufficient to have high sensitivity (77%) for detecting true functional connections (Smith et al., 2011). 7 FHP and 2 FHN youth were excluded from the resting state analyses due to excessive motion, while an additional FHP participant was excluded due to poor co-registration of functional and anatomical data, likely also a result of motion artifact. Between-group differences in the percentage of frames removed, as well as mean signal variation in the remaining subjects, was compared in the 16 FHP and 18 FHN adolescents with valid data using independent samples *t*-tests. Furthermore, multiple regression models were used to ensure that there was no group x

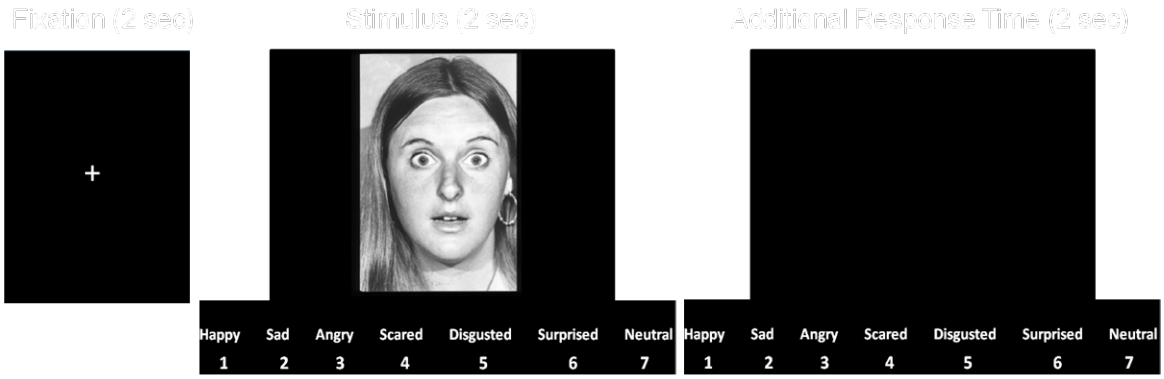
age interaction with respect to these motion parameters. Finally, an additional measure of frame-to-frame displacement (FD) (Power et al., 2012) for each participant's remaining frames was calculated using the following scalar formula: (FDi =|Δdix|+|Δdiy|+|Δdiz|+|Δαi|+|Δβi|+|Δγi|), where Δdix =d(i−1)x –dix, and is similar to the other displacement and rotational parameters. FHP and FHN youth were also compared with respect to mean remaining FD using a two-sample *t*-test.

2.8.3 *Image Analyses*

Functional connectivity of the left and right amygdala and the pre-defined ROIs (left and right DLPFC, left and right IPL, dACC), was examined using the following procedure. For identification of the amygdalar ROIs, each participant's anatomical data were transformed into Montreal Neurological Institute atlas space for processing by FSL's FIRST (Patenaude et al., 2011), as described in section 2.7.6. Once the amygdalar ROIs were segmented by FIRST, they were transformed back to Talairach space and visually inspected by A.C. in Caret, software Version 5.612 (Van Essen et al., 2001), which was also used to visualize fMRI data. All nuclei were properly defined by the program in the participants with valid resting state data. The ROIs of interest were defined by Talairach coordinates previously published in the literature (Fair et al., 2008; Fair et al., 2009) (fronto-parietal: L DLPFC: x = -43, y = 22, z =34, R DLPFC: x = 43, y = 22, z =34, L IPL: x = -51, y = -51, z = 36, R IPL: x = 51, y =-47, z = 42, cingulo-opercular: dACC: x = -1, y = 10, z = 46). Washington University's in-house software, fidl, was used to create 10 mm radius spheres around the peak coordinates of the ROIs listed above. Next, the functional connectivity maps and timecourses for these ROIs were obtained and correlation coefficients were extracted between each of the amygdalar nuclei and the five other cognitive control ROIs.

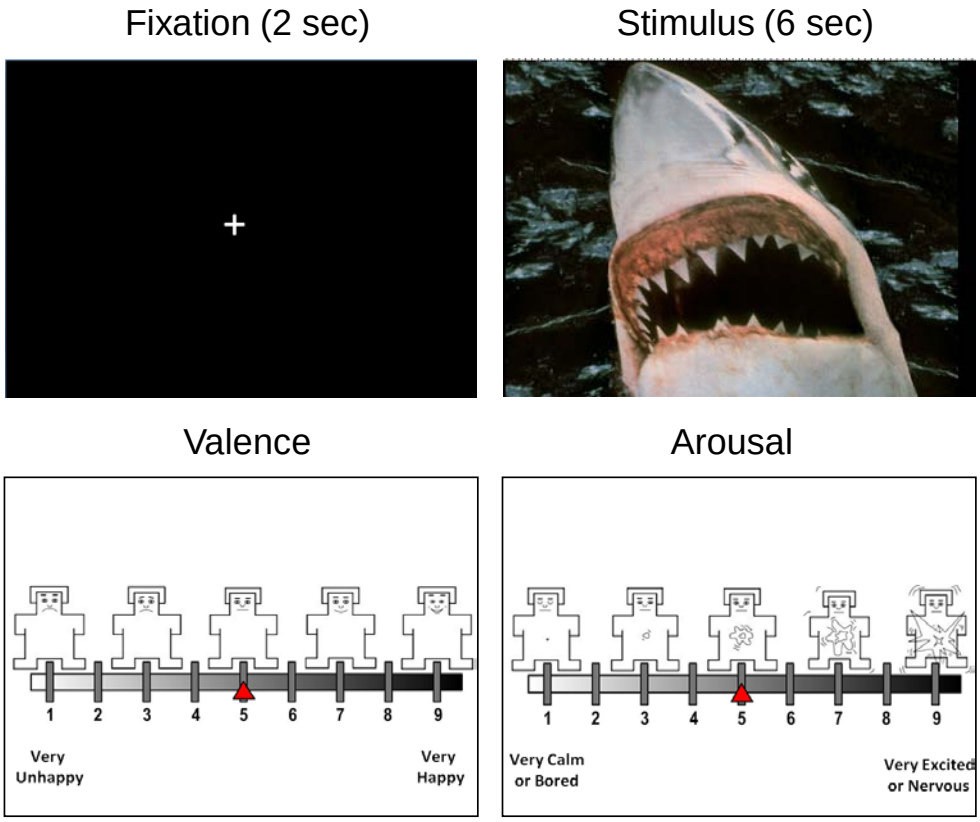
Additionally, a whole-brain connectivity analysis was also used to determine differences in amygdalar functional connectivity with other areas of the brain, not included in the *a priori* ROIs. For both FHP and FHN youth, resting state functional connectivity maps were generated by correlating the timecourse of the amygdalar ROIs with all other voxels in the brain. One-sample *t*-tests were performed to examine each group's functional connectivity patterns as well as a two-sample *t*-test (assuming unequal variance $p < 0.05$) to compare all possible whole-brain differences between FHP and FHN youth (comparing the Fisher *z* transformed *r*-values). Monte Carlo simulation was applied to estimate the number of contiguous voxels at $p < 0.05$ needed for cluster correction at $z > 2.25$, which resulted in a minimum cluster size of 53 voxels.

Figure 4. Emotion Recognition Task.



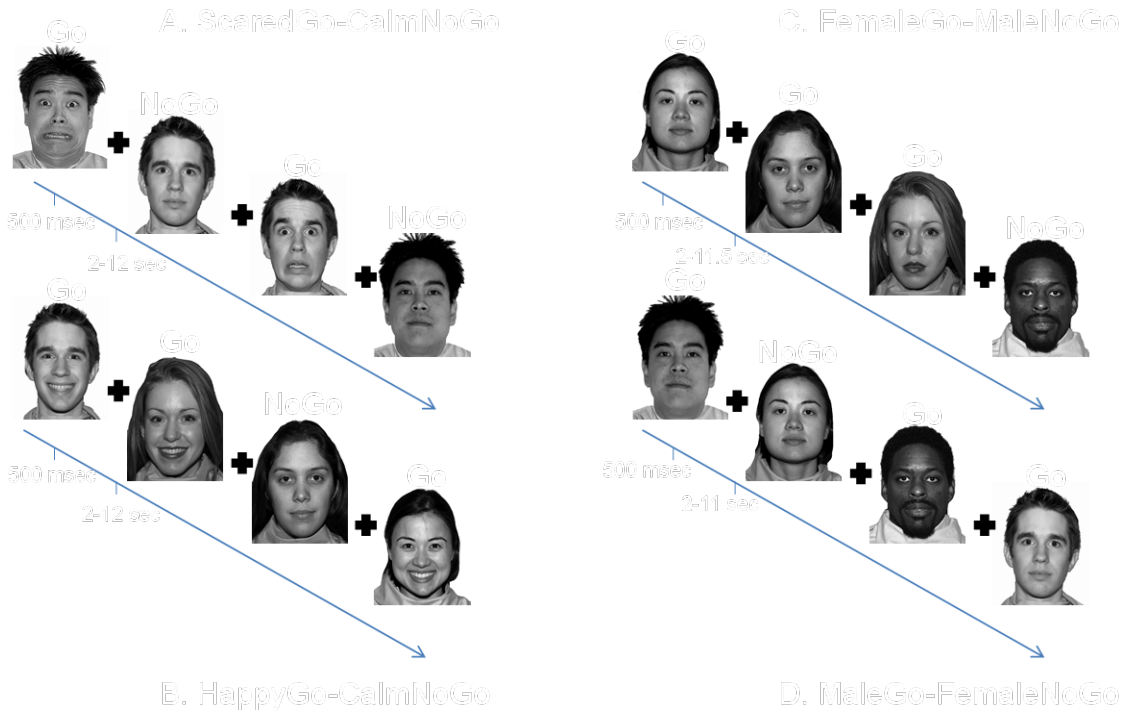
For the Emotion Recognition Task, participants were instructed to identify the emotion of the faces they saw. They were told to respond as quickly and as accurately as possible. A total of 4 seconds was allotted for the response times (2 seconds while the picture was present and 2 seconds afterwards). Responses not made within this time window were considered missed trials. A 2 second fixation period was the intertrial interval between each presentation of a face. A total of 56 randomized trials were presented, such that there were 8 appearances of each of the 7 emotions. Example picture from Ekman & Friesen, 1976.

Figure 5. Affective Rating Task.



For the Affective Rating Task, participants were instructed to look at the pictures and on the following screen first rate how unhappy or happy the picture made them feel, followed by another screen in which they needed to rate how calm/bored or excited/nervous the picture made them feel (scale of 1-9). The Self-Assessment Manikin was used to aid youth in rating their responses to the pictures. 45 stimuli (15 pleasant, 15 unpleasant, and 15 neutral) were presented in a randomized order for each participant. Each picture (example from Lang, Bradley, & Cuthbert, 2008) appeared on the screen for 6 seconds, followed by the rating scales, for which there was no time limit to respond. A 2 second fixation period was used as the intertrial interval.

Figure 6. Emotional Go-NoGo Task.



Adapted from Hare et al., 2008

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

CHAPTER 3. RESULTS

3.1 **Aim 1: Participant Characteristics**

Demographic variables were compared in the 24 FHP and 20 FHN youth included in the analyses of the Emotion Recognition and Affective Rating Tasks. Youth did not differ on age, IQ, SES, or pubertal stage (the latter assessed by either the PDS or Tanner line drawings). Further, FHP and FHN youth were very comparable in gender and racial make-up (**Table 1**). Gender distribution within each group was split almost equally between boys and girls, and Caucasian race closely resembled the percentage of white individuals (>80%) in the state of Oregon (United States Census Bureau).

In addition to demographic variables, a number of personality characteristics were assessed in youth (**Table 2**) to examine whether there were any group effects on these measures that may be related to task performance. There was no main effect of Group ($F_{5,38}$ = 1.27, p = 0.30, partial η^2 = 0.14) using MANOVA to examine the variables of interest, including PSS, CDI, ICU-Youth, ICU-Parent, and the UPPS-P-R-C. Mean T-scores on the CDI suggested below average depressive symptoms in each group, consistent with inclusion criteria. Scores on the PSS ranged from 14-70, with higher scores reflecting greater stress levels. Mean scores in FHP and FHN youth were in the low 30s, suggesting that on average, stress was below the 50th percentile in each of the groups. Mean ICU Total scores in FHP and FHN youth from both the youth and parent questionnaires were lower than the average scores in a large validation sample (>1000 youth) of 13-14 and 15-16 year old adolescents (mean scores 22.5 and 26.54 for these age groups, respectively) (Essau et al., 2006). Furthermore, the ICU-Youth and ICU-Parent Total scores were highly correlated across the entire sample of 44 youth (R^2 = 0.11, β = .34, t_{43} = 2.33, p = 0.03), although there was a lack of a statistically significant

relationship between these scores when either group was examined alone. Additionally, since sleep problems have been associated with substance use during adolescence (Wong et al., 2004; Wong et al., 2009) and atypical sleep patterns have been found in FHP youth (Dahl et al., 2003; Tarokh and Carskadon, 2010), the average of the sleepiness and sleep problems score from the SHQ was compared between groups. One youth from each of the groups had missing data on the questionnaire. Thus, 23 FHP and 19 FHN adolescents were compared for this measure. There was a trend for FHP youth to have greater sleepiness/sleep problems than FHN youth (t_{40} = 1.70, p = 0.097).

Family history density of psychopathology is presented in **Table 3**. FHD (as described in section 2.2.1) reflects the degree of familial alcoholism or other psychiatric disorders in youth, with higher scores reflecting greater density of the disorder. Family history of AUD in the FHP group ranged from weighted scores of 0.17-1.30. Fifty percent of FHP youth had biological fathers with a history of an AUD, 12.5% had biological mothers with alcoholism, 41.67% had grandparents with the disorder, and 66.67% had an aunt or uncle who met AUD criteria. FHD of mood disorders ranged from 0 in each group to 0.75 and 1.46 in FHN and FHP youth, respectively. FHP youth had significantly higher density of familial mood disorders than FHN youth, and this was driven by a statistically significant difference in familial MDD between the groups, as there was no group difference in familial GAD. Not surprisingly, SIMD differed between FHP and FHN youth, and there was a trend for family history of ASPD to be more prevalent in FHP youth than their peers.

As ensured by the exclusionary criteria of this study, all youth had minimal experience with alcohol or other substances (marijuana and cigarettes). The number of youth who had ever used alcohol, marijuana, or cigarettes, lifetime occasions of use,

and drinks/occasion for alcohol are listed in **Table 4**. As there was no history of self-reported neurotoxic levels of alcohol or substance use in any of the adolescent participants, results of the behavioral and brain imaging experiments are likely not attributable to the effects that heavy alcohol or substance use may have on adolescent brain and behavior.

Due to small to moderate effect sizes (Cohen's *d*: 0.04 – 0.34), in addition to the lack of statistically significant group differences on the nuisance variables, none were included as covariates for the analyses of this aim.

3.2 Aim 1: Emotion Recognition Task

Since FHP and FHN youth significantly differed on the Family History of Mood Disorders Composite score, with FHP youth having higher density of familial mood disorders, this variable was correlated with accuracy and reaction time from the ERT, to examine whether there was any relationship between familial mood disorders and task performance. FHD of mood disorders did not relate to any measure of accuracy or reaction time on the ERT. Thus, it was not included as a covariate for the mixed model design described below.

There were no significant group differences in mean accuracy (FHP = 70.79%, FHN = 71.84%, t_{42} = .25, p = 0.80) or mean reaction time (FHP = 1928.02 ms, FHN = 1907.67 ms, t_{42} = .44, p = 0.66) during recognition across the seven different emotional expressions. Further, FHP and FHN youth did not differ in the number of missed responses across any of the emotional faces presented in the task (all p's > 0.1), suggesting comparable levels of attention and motivation during the task. 2 x 7 ANOVAs were used to examine main effects of Emotion (Happy, Sad, Angry, Scared, Disgusted, Surprised, Neutral), Group (FHP and FHN), and the interaction of Emotion x Group on recognition accuracy and reaction time on correct trials (**Figure 7**). There was a

statistically significant main effect of Emotion ($F_{6,252}$ = 46.13, *MSE* = 3.65, p = 0.00, partial η^2 = 0.52), but no significant effect of Group and no Group x Emotion interaction on recognition accuracy, although the latter was trend-level ($F_{6,252}$ = 2.02, *MSE* = 3.65, p = 0.065, partial η^2 = 0.046). The significant effect of Emotion on accuracy was followed up with pairwise *t*-tests, which indicated that overall, youth were better at recognizing Happy, Surprised, and Neutral faces as compared with Sad, Angry, Scared, and Disgusted faces. Happy faces were better recognized than all other faces, except for Neutral expressions. Sad, Angry, and Disgusted faces could be better recognized than Scared faces, which had the overall poorest recognition accuracy (all p's < 0.05/21, Bonferroni corrected for multiple comparisons). To ensure that lack of detecting a significant interaction was not due to low power for the analyses, GPower 3.1 (Faul et al., 2007) was used to estimate achieved power based on an alpha level of 0.05, the effect size, and the sample size of the analyses. The achieved power $(1 - \beta) = 0.898$ for the interaction indicates that lack of an effect for this analysis was not due to weak power, but rather a weak effect.

For the analysis of reaction time, there was again a statistically significant main effect of Emotion ($F_{5.51,198}$ = 52.81, *MSE* = 100694, p = 0.00, partial η^2 = 0.60), but no significant Group or Group x Emotion effects. Analyses of simple effects for the significant main effect of Emotion on reaction time indicated that youth were overall faster when correctly identifying Happy faces as compared with all other faces, and quicker to identify Neutral faces than Angry, Scared, Disgusted, or Surprised faces. Sad expressions were also more quickly recognized than Angry, Scared, Disgusted, and Surprised expressions (all p's < 0.05/21, Bonferroni corrected for multiple comparisons). Furthermore, a within-group analysis in FHP youth indicated that FHD of AUD did not correlate with accuracy or reaction time for any of the seven emotions.

3.3 Aim 1: Affective Rating Task

FHD of mood disorders did not relate to any of the valence or arousal ratings on the ART, so it was not included as a covariate for the mixed model design described below.

Two 2 x 3 ANOVAs were used to analyze the effects of Picture (Pleasant, Neutral, Unpleasant), Group (FHP and FHN), and Group x Picture interactions on valence and arousal ratings (**Figure 8**). For valence ratings, there was a significant main effect of Picture ($F_{1.33,55.71}$ = 277.98, *MSE* = 1.11, p = 0.00, partial η^2 = 0.87), but no Group effect or Group x Picture interaction. As might be expected, pairwise *t*-tests indicated that Pleasant pictures made youth feel significantly more happy than Neutral pictures, and Neutral pictures were rated higher on valence than Unpleasant pictures (all p's < 0.05/3, Bonferroni corrected for multiple comparisons). Similarly for arousal ratings, there was a significant main effect of Picture ($F_{2,84}$ = 70.23, *MSE* = 1.70, p = 0.00, partial η^2 = 0.63), but no Group effect or Group x Picture interaction. Pleasant and Unpleasant pictures were not surprisingly significantly more arousing than Neutral pictures (all p's < 0.05/3, Bonferroni corrected for multiple comparisons). Finally, familial density of AUD in the FHP youth was examined to see if it correlated with any of the valence and arousal measures. There was a significant correlation between FHD of alcoholism and ratings of arousal to Pleasant pictures, such that higher family density was associated with lower ratings of arousal (R^2 = .18, β = -.43, p = 0.04). However, even after applying the more liberal FDR correction for multiple correlations (as opposed to Bonferroni), this effect was not significant.

In summary, the hypotheses of the first aim were not supported, as there was a failure to detect group differences on emotion recognition accuracy or subjective affective ratings between FHP and FHN youth.

3.4 Aim 2: Participant Characteristics

19 FHP and 17 FHN youth met the minimum performance criteria on the Emotional Go-NoGo task to be included in the fMRI analyses. Five FHP and three FHN youth were excluded because they did not meet the performance criteria on the task. Chi square test indicated that there were no significant group differences with respect to the number of youth excluded from the imaging analyses ($X^2_1 = 0.25$, $p = 0.62$). Youth in this smaller sample did not differ on age, IQ, SES, or pubertal stage, assessed by either the PDS or Tanner line drawings. Further, FHP and FHN youth were very similar in gender and racial make-up (**Table 5**). No nuisance variables differed significantly between FHP and FHN youth, and all group differences had small to moderate effect sizes (Cohen's *d:* 0.19 – 0.39), so none were included as covariates for the fMRI analyses.

To verify the comparability of personality characteristics between this sample and the larger sample used in the behavioral analyses, a MANOVA was performed again to examine whether there was a main effect of Group on the variables of interest (**Table 6)**. There was no main effect of Group, so further univariate tests were not performed ($F_{5,30}$ = 1.71, $p = 0.16$, partial $\eta^2 = 0.22$). Youth also did not differ in pre-scan state anxiety levels ($t_{34} = 1.31$, $p = 0.20$). In this smaller sample used for fMRI analyses, FHD of MDD, GAD, SIMD, or the mood disorders composite score did not significantly differ between FHP and FHN youth (**Table 7**).

3.5 Aim 2: Emotional Go-NoGo Task Behavior

Behavior on the Emotional Go-NoGo task is reported in **Table 8**. To avoid Type I error, hits, correct rejections, reaction time, and d-prime were analyzed using a 2 x 3 MANOVA, with Emotion (Happy, Scared, Calm) as the within-subjects factor and Group (FHP, FHN) as the between-subjects factor. A statistically 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 x Group effects. Thus, the latter two effects were not analyzed further in the subsequent univariate models for each of the dependent variables. However, the effect of Emotion was examined on hits, correct rejections, reaction time, and d-prime using mixed model ANOVAs. Univariate models showed a significant effect of Emotion on reaction time ($F_{2,68}$ = 21.34, *MSE* = 2241.44, p = 0.00, partial η^2 = 0.39) and d-prime ($F_{2,68}$ = 5.32, *MSE* = 0.25, p = .00, partial η^2 = 0.14), but not hits or correct rejections (p = 0.06). Simple effects for the ANOVA examining reaction time showed that overall, reaction time was faster on Go trials when Happy or Calm faces were presented (p = 0.00), compared with Scared faces. Additionally, the simple effect analysis for d-prime, indicated that signal detection for runs with HappyGo trials and CalmNoGo trials was significantly higher than d-prime for runs with ScaredGo trials and CalmNoGo trials (p = 0.006), but not runs in which target (Go) and distractor (NoGo) faces were all Calm (p = 0.063), though the latter was at trend-level. Furthermore, it should be noted that there were no significant Group or Group x Emotion effects when a MANOVA was run on the entire sample of 24 FHP and 20 FHN youth. The only significant multivariate effect was for Emotion ($F_{8,33}$ = 8.98, p = 0.00, partial η^2 = 0.69). This suggests that despite the sample size being smaller for the imaging analyses, the behavioral data was comparable when the sample was restricted based on performance to increase power for the fMRI analyses.

The results of the computerized exit questionnaire examined youths' response to the faces seen during the task using ratings of valence and arousal (**Table 12**). 2 x 3 ANOVAs examined the effect of Emotion (Happy, Scared, Calm), Group (FHP and FHN), as well as the interaction of Emotion x Group on these measures. There was a main effect of Emotion for both valence and arousal ($F_{2,68}$ = 37.22, *MSE* = 0.94, p = 0.00, partial η^2 = 0.52 ;$F_{2,68}$ = 29.97, *MSE* = 1.2, p = 0.00, partial η^2 = 0.47), but no main

effect of Group and no interaction for either measure. Simple effects showed significantly higher ratings on valence for Happy compared with Scared or Calm faces ($p < 0.05/3$, Bonferroni corrected for multiple comparisons). Additionally, simple effects indicated significantly higher arousal on Happy and Scared faces vs. Calm faces ($p < 0.05/3$, Bonferroni corrected for multiple comparisons).

3.6 **Aim 2: Emotional Go-NoGo Brain Activity**

Two FHP and two FHN youth had TRs censored due to excessive head motion during the task (FHP: 4 and 12 TRs; FHN: 2 and 10 TRs). No youth had mean RMS values > 1.5 mm across the task. FHP and FHN youth did not differ on the number of TRs censored ($U_{34} = 160.5$, $Z = -0.058$, $p = 0.98$) or mean RMS across the task (FHP = 0.23±.04, FHN = 0.24±.04, $t_{34} = .18$, $p = 0.86$), indicating that the groups were very similar in overall movement during scanning. To examine the BOLD response, task-related brain activity was first analyzed for each group using one-sample *t*-tests (**Tables 9 and 10; Figures 9 and 10**).

3.6.1 *Neural Reactivity to Emotional Faces in FHP and FHN Youth*

Both FHP and FHN youth showed greater brain activity to positively valenced emotional faces (Happy vs. Calm) in widespread areas of the visual cortex, temporal lobes, frontal lobes, as well as areas of the basal ganglia and insula. Neither group showed greater activation to Calm faces than Happy faces (**Table 9**). Similar patterns of brain activity were seen when comparing the response to negatively valenced emotional faces (Scared vs. Calm) for each of the groups (**Table 9**), such that there was greater activity to Scared faces. However, FHP youth showed deactivation to Scared faces in the superior parietal lobule (SPL), bilateral postcentral gyri, precuneus, and cuneus.

3.6.2 *Inhibitory Control Brain Activity in FHP and FHN Youth*

Individual group activation during inhibitory control is reported in **Table 10**. Both FHP and FHN youth showed deactivation in superior, middle, and inferior frontal gyri, ACC, and insula during response inhibition (CalmNoGo trials) within a positively valenced emotional context (HappyGo trials). However, FHN youth also had greater activity during response inhibition in the positive emotional context in a cluster that included pre- and postcentral gyri, the parietal lobe, and portions of the frontal cortex. Inhibitory control activity in the negatively valenced emotional context (ScaredGo trials) was reduced in widespread areas of the frontal lobe in FHP youth, including superior, middle, and inferior frontal gyri, the ACC, and basal ganglia. In FHN youth, only two clusters showed differences in activation between the different inhibitory conditions. Right SPL showed less activity during response inhibition in the negative emotional context (ScaredGo trials), while the right cuneus showed more activity in the emotionally neutral condition (CalmGo trials).

3.6.3 *Differences in Brain Response to Emotional Faces Between FHP and FHN Youth*

Between-group differences in neural reactivity to emotional faces and inhibitory control are reported in **Table 11**. There were statistically significant group differences on brain response to positively valenced faces, but not negatively valenced faces. Specifically, FHP youth, showed less activity to Happy faces in two clusters that included areas of the left STG, left insula, and left postcentral gyrus. **Figure 11** illustrates this group difference in brain activity along with bar graphs illustrating percent signal change in the two clusters for the contrast of interest, as well as each of the components of the contrast (HappyGo and CalmGo trials). Mixed model ANOVAs examined the effect of Emotion (Happy and Calm), Group (FHP and FHN), and the Group x Emotion interaction. In both of these clusters, there was a significant interaction effect ($F_{1,34}$ = 14.0, *MSE* = 0.01, p = 0.001, partial η^2 = 0.29; $F_{1,34}$ = 19.1, *MSE* = 0.01, p = .00, partial

η^2 = 0.36). Examination of the interaction showed that FHP youth had significantly less activity to positive emotional valence (Happy faces) compared with FHN youth (p < 0.05). In the smaller cluster, FHP youth also had significantly greater activity during the emotionally neutral condition (Calm faces) than FHN youth (p < 0.05), and this pattern was a trend in the larger of the two clusters (p = 0.096). There were no significant group differences in response to negatively valenced faces.

The hypotheses of this aim were not supported, as FHP youth did not differ from their peers in brain response to negatively valenced faces. While not originally predicted, FHP youth did show blunted superior temporal cortex activity to positively valenced faces compared with their peers.

3.6.4 *Differences in Inhibitory Control Brain Activity Between FHP and FHN Youth*

Figure 12 illustrates statistically significant differences in brain activity during cognitive inhibitory control in FHP and FHN youth. **Table 11** indicates that during response inhibition (CalmNoGo trials) in the positively valenced emotional context, FHP youth showed less brain activity in superior and middle frontal gyri than FHN youth. Mixed model analysis indicated an interaction ($F_{1,34}$ = 33.14, MSE = 0.02, p = 0.00, partial η^2 = .49, and $F_{1,34}$ = 10.08, MSE = .34, p = .003, partial η^2 = 0.23), such that FHP youth significantly deactivated these regions during response inhibition in the positively valenced emotional context compared with their peers (p's < 0.05). In the larger of the two clusters, FHP youth also showed more activity during inhibition in the neutral emotional context (when target faces were Calm) compared with FHN youth (p < 0.05), with both groups showing positive activation during inhibitory control (**Figure 12A**). Finally, during inhibitory control in the negatively valenced emotional context, FHP youth showed significant deactivation in seven clusters compared with FHN youth. The majority of these clusters were in regions that are part of the fronto-parietal and cingulo-

opercular networks, with the exception of the parahippocampal gyrus (**Table 11/Figure 12B**). Mixed model ANOVAs showed a significant interaction of Emotion and Group in all seven clusters (all p's < 0.01, partial η^2 range = 0.24 – 0.41). Examination of simple effects indicated that in all of these regions, FHP youth had reduced brain response during inhibition (CalmNoGo trials) within the negatively valenced emotional context compared with FHN youth (p's < 0.05). Additionally, in two of the seven clusters FHP youth showed more activity during inhibition during the neutral emotional context (Calm target faces), compared with their peers (p's < 0.05).

Finally, FHD of alcoholism was correlated with the BOLD signal in the regions of group differences in activation. There was a significant relationship between FHD and deactivation in the left MFG (cluster 5 in **Figure 12**), indicating that greater FHD of alcoholism was associated with reduced brain response during inhibition in the negative emotional context (R^2 = 0.42, β = -0.65, p = 0.003).

Hypotheses of this aim were supported, since FHP youth showed reduced cognitive control brain activity in the negative emotional context compared with their peers, which was reflected in reduced frontal, striatal, and parietal brain response. In addition, while not originally hypothesized, a similar effect was seen during response inhibition in the positively valenced emotional context in superior/middle frontal gyri.

3.6.5 *Region of Interest Analyses*

Independent-samples *t*-tests indicated no statistically significant group differences in amygdalar activation in either of the contrasts comparing emotional reactivity to faces. ROI analyses were also performed for the left and right fusiform gyrus with the same voxel and cluster correction (20 and 19 contiguous significant voxels for left and right fusiform gyus, respectively). These ROIs were defined using AFNI's

Talairach Daemon tool. No significant group differences in brain activity were found for either emotionally valenced condition in these regions.

3.6.6 *fMRI Task Exit Questionnaire*

Participants completed a 4-item questionnaire at the end of the fMRI scan to assess self-report on task motivation, difficulty, perception of performance, and emotional reactivity to faces (Appendices). For both FHP and FHN youth, the most common responses for each of the 4 questions were identical. The most frequent response to task motivation was moderate level of importance to do well. The task was rated as "a little difficult" for each group, while most participants believed they did well on the task. Most youth reported little to no emotional reaction to the faces they saw. Greater than 50% of youth responded with these answers for each of the questions in both groups. Mann-Whitney U-tests showed no group differences in responses to any of the questions.

3.7 **Aim 3: Participant Characteristics**

Analyses of rs-fcMRI for the amygdala included 16 FHP and 18 FHN adolescents after exclusion of participants due to excessive head movement. Chi square test showed that there was a trend for a greater number of FHP than FHN youth who were excluded from the resting state imaging analyses due to movement or co-registration errors (X^2_1 = 3.38, p = 0.07). However, the adolescents included in the final sample, were very well matched on percent frames removed, mean DVAR, and mean FD (**Table 16**). They were also matched on most demographic variables (**Table 13**), personality characteristics of interest (**Table 14**) (MANOVA: ($F_{5,28}$ = 0.82, p = 0.54, partial η^2 = 0.13), pre-scan anxiety (t_{32} = 1.64, p = 0.11), and family history density of psychiatric disorders (**Table 15**). No nuisance covariates differed significantly between FHP and FHN youth and all group differences had small to moderate effect sizes (Cohen's *d:* 0.06 – 0.30), so none were

included as covariates for the resting state connectivity analyses. There was a trend for FHP youth to have higher family history density of MDD, as well as a higher overall family history of mood disorders composite score than FHN youth.

3.8 Aim 3: Amygdalar Resting State Functional Connectivity with *a priori* ROIs

The first analysis of rs-fcMRI compared FHP and FHN youth on differences in spontaneous fluctuations of the BOLD response between the left and right amygdala and *a priori* hypothesized seed regions. There were no statistically significant between-group differences in the connectivity of left and right amygdala and the *a priori* hypothesized ROIs, FDR corrected at $p < 0.05$ (**Table 17**).

3.9 Aim 3: Whole-Brain Amygdalar Resting State Functional Connectivity

The second approach for examining differences in amygdalar functional connectivity used a whole-brain connectivity analysis. Specifically, FHP and FHN youth were compared on left and right amygdalar functional connectivity with all other voxels in the brain. Both left and right amygdala showed between-group differences in connectivity, corrected for multiple comparisons using Monte Carlo simulation, at the voxel and cluster level ($p < 0.05$, ≥ 53 contiguous voxels). This analysis resulted in 7 ROIs in which there were group differences in left amygdalar functional connectivity, and 3 ROIs that differed in right amygdalar functional connectivity between FHP and FHN youth (**Table 18**). Specifically, FHP and FHN youth differed in left amygdalar connectivity with two clusters in the left superior frontal gyrus (SFG), one cluster in the right MFG, two clusters in the cerebellum, one in the left precuneus, and one 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). The patterns of functional connectivity between the amygdalar seeds and these 10 ROIs are illustrated in **Figure 13**, which indicates whether the BOLD response fluctuations in the amygdalar seeds are

positively or negatively connected to the spontaneous activity of the brain regions showing group differences.

3.9.1 *Left Amygdala*

Compared with FHN adolescents, FHP youth had more negative functional connectivity or greater segregation between the left amygdala and three ROIs in the frontal lobe, including two clusters in the left SFG and one in the right MFG. FHP youth had positive connectivity between the left amygdala and the left cerebellum, but negative connectivity with the right cerebellum, while FHN youth showed opposite patterns of connectivity in both of these regions. FHP youth had negative functional connectivity between the left amygdala and the left precuneus, while FHN youth showed positive connectivity to this region. Finally, FHP youth showed positive connectivity to the right precentral gyrus, while FHN youth showed negative functional connectivity to this area.

3.9.2 *Right Amygdala*

FHP youth had greater segregation, or greater negative connectivity, between the right amygdala and right MFG, compared with FHN youth. They also showed segregation (negative correlations) between the right amygdala and right MTG, while FHN youth showed integration (positive correlations) between these regions. Finally, FHP youth showed positive functional connectivity between the right amygdala and the right cerebellum, while FHN youth had negative connectivity between these regions.

3.10 **Aim 3: Signal-to-Noise Ratios in Left and Right Amygdala**

Subcortical regions, such as the amygdala, are particularly sensitive to signal dropout in echo-planar imaging (LaBar et al., 2001). Thus, it is important to know whether FHP and FHN youth may have differed in signal-to-noise ratio (SNR) in the left and right amygdalar ROIs that could have accounted for any of the significant group differences in connectivity observed. The BOLD signal from the left and right amygdalar

ROIs were extracted from the original T2* weighted EPI images. SNR were then calculated by averaging the signal across each amygdalar ROI and dividing it by the average signal extracted from a region with minimal susceptibility artifact (a 10 mm diameter sphere located in the left DLPFC: x = -43, y = 22, z = 34). FHP and FHN youth did not show any significant differences in SNR for either amygdalar ROI (left: FHP mean = 0.66, SD = 0.14, range = 0.47 to 0.92; FHN mean = 0.66, SD = 0.14, range = 0.41 to 0.88; t_{32} = 0.11, p = 0.91); (right: FHP mean = 0.69, SD = 0.13, range =0.50 to 0.92; FHN mean = 0.71, SD = 0.13, range = 0.43 to 0.93; t_{32} = 0.37, p = 0.71).

3.11 Aim 3: Resting State Functional Connectivity and Task Behavior Relationships

Given the statistically significant differences between FHP and FHN youth in whole-brain amygdalar connectivity, the next step of this analysis investigated whether differences in intrinsic BOLD response were related to behavioral phenotypes in these youth. The consistent negative connectivity found between both left and right amygdalar seeds and regions of the PFC, suggested weaker cortico-limbic functional connectivity in FHP youth. Since the Emotional Go-NoGo task required participants to exert inhibitory control during trials embedded in different emotional conditions, 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, a measure of inhibitory control accuracy, was correlated with the Fisher's *z*-scores in the prefrontal cortical ROIs in which group differences in connectivity were observed.

This was done by extracting the correlation coefficients from the ROIs of group difference for each subject in both the FHP and FHN youth. Pearson correlations were then used to correlate the Fisher's *z*-scores in these ROIs with the number of correct rejections during the emotionally and neutrally valenced runs of the task. Two significant

correlations, as well as a trend between correct rejections and left amygdala-left SFG connectivity was found for the FHP youth, whereas no relationship between left amygdala-left SFG connectivity was found for the FHN youth. Specifically, for correct rejections during the positively valenced emotional context and neutrally valenced context, greater segregation (or negative connectivity) between the amygdala and SFG was related to poorer inhibitory control (HappyGo/CalmNoGo: $r = 0.72$, $p = 0.002$; CalmGo/CalmNoGo: $r = 0.66$, $p = 0.005$), and a trend relationship was also seen for this association during the negatively valenced emotional context ($r = 0.46$, $p = 0.07$).

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 (or a greater number of correct rejections) during the HappyGo/CalmNoGo run was predictive of increased connectivity between the left amygdala-left SFG (Monte Carlo corrected, $z = 2.25$, ≥ 53 voxels). A conjunction analysis was performed to analyze the overlap of this correlation map with the group differences in connectivity between the left amygdala-left SFG. This conjunction analysis indicated that a region with cluster size of 11 voxels showed significant group differences in connectivity and was also related to task performance in FHP youth.

Finally, correlations of FHD of alcoholism and resting state BOLD signal were examined in the clusters of group difference, but no significant relationships were found. Since FHD of MDD was marginally greater in FHP youth than their peers, hierarchical regressions were performed to covary for FHD of MDD in the resting state analyses. Covarying for these group differences in FHD of MDD, suggested that in one region of resting state amygdalar group differences, FHD of MDD was a significant predictor ($R^2 = 0.16$, $\beta = -0.40$, $t = -2.46$, $p = 0.02$). However, even after controlling for this covariate, the group effect was still significant, indicating greater negative connectivity between the left

amygdala and left precuneus in FHP compared with FHN youth (R^2 = 0.38, β = -0.49, t = -3.32, p = 0.002).

The findings from this aim of the dissertation supported the hypotheses, which predicted that FHP youth would show reduced amygdala to PFC resting state functional connectivity compared with their peers. However, these group differences were detected using whole-brain functional connectivity analyses, but not with the *a priori* defined ROIs. Furthermore, this negative functional connectivity in FHP youth was also related to task performance. Specifically, intrinsic BOLD fluctuations between the left amygdala and left SFG that were weaker in FHP youth were correlated with response inhibition during the Emotional Go-NoGo task, such that reduced connectivity between these regions in FHP youth was related to poorer inhibitory control.

Table 1. Participant Demographics. Means and standard deviations unless otherwise noted.

	FHP	FHN	Statistic	*p* value
N	24	20		
Age	14.75(1.42)	14.70(1.24)	$t_{42} = .12$	.90
Gender	11F/13M	9F/11M	$X^2_1 = .003$	.96
Caucasian (%)	87.5	80	$X^2_1 = .46$	.50
IQ[a]	112.0(10.48)	111.45(10.22)	$t_{42} = .07$	.95
SES[b]	30.96(12.25)	28.30(13.20)	$t_{42} = .69$	.49
PDS[c] Crockett Stage	3.71(1.0)	3.60(.68)	$U_{42} = 207.5$ $Z = .85$	.40
Tanner Stage	3.83(1.13)	4.15(.67)	$U_{42} = 211.5$ $Z = .72$	.47

[a]Wechsler Abbreviate Scale of Intelligence (transformed)
[b]Hollingshead Index of Social Position; lower values indicate higher SES; Means for FHP and FHN youth correspond to upper middle class.
[c]Pubertal Development Scale

Table 2. Participant Personality Characteristics. Means and standard deviations unless otherwise noted.

	FHP	FHN
N	24	20
CDI[a] T-score	42.96(5.81)	41.40(6.18)
Perceived Stress Scale	33.83(6.36)	32.95(6.42)
UPPS-P-R-C[b] Scale Total	2.74(.36)	2.93(.34)
ICU[c]-Youth Total	19.42(5.01)	17.05(8.06)
ICU-Parent Total	21.83(8.06)	16.7(5.35)

[a]Children's Depression Inventory
[b]UPPS-P Impulsive Behavior Scale for Children; lower values indicate greater impulsivity.
[c]Inventory of Callous-Unemotional Traits

No statistically significant Group effect ($F_{5,38}$ = 1.27, p = 0.30, partial η^2 = 0.14) for the MANOVA examining these variables.

Table 3. Family History Density of Alcohol Use Disorders, Mood Disorders, and Antisocial Personality Disorder. Means and standard deviations unless otherwise noted.

	FHP	FHN	Statistic	*p* value
N	24	20		
Family History AUD[a]	0.61(.25)	0		
Family History MDD[b]	0.28(.29)	0.14(.24)	U_{42} = 152, Z = 2.21	**.03**
Family History GAD[c]	0.07(.19)	0.09(.19)	U_{42} = 233, Z = .25	.81
Family History SIMD[d]	0.07(.16)	0		
Family History ASPD[e]	0.08(.18)	0.004(.02)	U_{42} = 189.5, Z = 1.87	.06
Family History Mood Composite[f]	0.36(.37)	0.18(.24)	U_{42} = 152, Z = 2.15	**.03**

[a]Alcohol Use Disorder
[b]Major Depressive Disorder
[c]Generalized Anxiety Disorder
[d]Substance Induced Mood Disorder
[e]Antisocial Personality Disorder
[f]Mean Scores of Major Depressive Disorder, Generalized Anxiety Disorder, and Substance Induced Mood Disorder (relatives with co-morbid mood disorders are not weighted more heavily); 3 FHP and 2 FHN youth had relatives with co-morbid mood disorders.

Bold *p*-values indicate statistically significant group differences.

Table 4. Minimal Substance Use in Participating Youth. Means unless otherwise noted.

	FHP	FHN
N	24	20
Alcohol Use (N)	1	3
Lifetime Alcohol Occasions	2	1.67
Drinks/Occasion	1	1.33
Marijuana Use (N)	5	3
Lifetime Marijuana Occasions	1.6	2.33
Nicotine Use (N)	2	1
Lifetime Nicotine Occasions	1.5	1

Table 5. Participant Demographics for Youth with Valid fMRI Data. Means and standard deviations unless otherwise noted.

	FHP	FHN	Statistic	*p* value
N	19	17		
Age	14.92(1.34)	14.69(1.10)	$t_{34} = .55$	.58
Gender	10F/9M	7F/10M	$X^2_1 = .47$	.49
Caucasian (%)	89.47	82.35	$X^2_1 = .38$	.54
IQ[a]	110.84(10.86)	113.29(9.19)	$t_{34} = .73$	.47
SES[b]	32.0(11.49)	27.12(13.70)	$t_{34} = 1.16$	.25
PDS[c] Crockett Stage	3.79(.98)	3.53(.72)	$U_{34} = 120$ $Z = 1.46$	.20
Tanner Stage	3.89(1.10)	4.12(.70)	$U_{34} = 151.5$ $Z = .34$	.75

[a]Wechsler Abbreviate Scale of Intelligence
[b]Hollingshead Index of Social Position
[c]Pubertal Developmental Scale

Table 6. Participant Personality Characteristics for Youth with Valid fMRI Data. Means and standard deviations unless otherwise noted.

	FHP	FHN
N	19	17
CDI[a] T-score	43.47(6.27)	40.06(3.60)
Perceived Stress Scale	33.74(7.05)	31.82(5.58)
UPPS-P-R-C[b] Scale Total	2.69(.31)	2.98(.28)
ICU[c]-Youth Total	18.89(4.61)	16.59(6.80)
ICU-Parent Total	20.89(8.64)	16.71(5.42)

[a]Children's Depression Inventory
[b]UPPS-P Impulsive Behavior Scale for Children; lower values indicate greater impulsivity.
[c]Inventory of Callous-Unemotional Traits

No statisticall significant Group effect for the MANOVA ($F_{5,30}$ = 1.71, p = 0.16, partial η^2 = 0.22) examining these variables.

Table 7. Family History Density of Alcohol Use Disorders, Mood Disorders, and Antisocial Personality Disorder for Youth with Valid fMRI Data. Means and standard deviations unless otherwise noted.

	FHP	FHN	Statistic	*p* value
N	19	17		
Family History AUD[a]	0.60(.27)	0		
Family History MDD[b]	0.24(.31)	0.15(.25)	U_{34} = 117, Z = 1.53	.17
Family History GAD[c]	0.06(.18)	0.10(.20)	U_{34} = 149.5, Z = .55	.71
Family History SIMD[d]	0.05(.13)	0		
Family History ASPD[e]	0.07(.17)	0.005(.02)	U_{34} = 135.5, Z = 1.37	.42
Family History Mood Composite[f]	0.30(.36)	0.19(.26)	U_{34} = 122, Z = 1.31	.22

[a]Alcohol Use Disorder
[b]Major Depressive Disorder
[c]Generalized Anxiety Disorder
[d]Substance Induced Mood Disorder
[e]Antisocial Personality Disorder
[f]Mean Scores of Major Depressive Disorder, Generalized Anxiety Disorder, and Substance Induced Mood Disorder (relatives with co-morbid mood disorders are not weighted more heavily); 3 FHP and 2 FHN youth had relatives with co-morbid mood disorders.

Table 8. Performance on the Emotional Go-NoGo Task. Means and standard deviations unless otherwise noted.

	FHP	FHN
N	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 (ms)		
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(.83)	3.33(.63)
Scared	2.89(.92)	3.14(.63)
Calm	2.83(.62)	2.74(.76)

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

A significant multivariate effect of Emotion was found ($F_{8,27}$ = 7.41, p = 0.00, partial η^2 = 0.69). Further examination of univariate models showed a significant effect of Emotion on reaction time ($F_{2,68}$ = 21.34, MSE = 2241.44, p = 0.00, partial η^2 = 0.39) and d-prime ($F_{2,68}$ = 5.32, MSE = 0.25, p = .00, partial η^2 = 0.14), but not hits or correct rejections (p = 0.06).

Table 9. Within-group results for *Go Contrasts*. Peak location, regions included, voxel number, and peak Talairach Coordinates are provided for each cluster.

Peak Anatomic Location	Regions Included	# Voxels	*x*	*y*	*z*
Go Brain Activity Within Groups					
FHP					
Happy > Calm					
L Lingual Gyrus	R LG, FG, IOG, thalamus, BG, PCC, PG	3099	-8	-95	-4
L MeFG	R MeFG, L STG, IFG, SFG, ACC, MFG, caudate	1095	-8	53	-16
L Postcentral Gyrus	L precentral gyrus, L insula, L cingulate, L precuneus	654	-53	-20	51
R SFG	L SFG, MeFG, CG, MFG	297	5	-5	66
R MFG	R insula, R precentral gyrus, R IFG	286	38	-5	63
Happy < Calm					
None					
FHN					
Happy > Calm					
R ITG	LG, FG, PG, MOG, IOG, insula, cuneus, precuneus, cingulate thalamus, putamen, R TG, pre/post-central gyrus	7505	50	-2	-31
L ITG	L FG, L TG, L PG, L insula L postcentral gyrus, L IPL	906	-47	-14	-37
L SFG	L MFG, L MeFG, R SFG	525	-17	50	45
Happy < Calm					
None					
FHP					
Scared > Calm					
R Thalamus	L thalamus, BG, IFG, MFG, insula pre/postcentral gyrus, brainstem	2627	2	-17	3
R Cuneus	L cuneus, PCC, precuneus, R FG	869	26	-92	-24
L SFG	ACC, MeFG	303	-14	29	54
Scared < Calm					
R Postcentral Gyrus	L postcentral gyrus, SPL, precuneus, cuneus	688	-2	-32	81
FHN					
Scared > Calm					
R STG	R MTG, IFG, SFG, MFG, MeFG R precentral gyrus, R cingulate	3004	35	8	-40
R MOG	R MTG, R STG, R LG, R FG, R MOG, R insula, R cuneus, R PG	1329	29	-89	12
L IOG	L MOG, L LG, L cuneus	544	-41	-86	-13
L Precentral Gyrus	L postcentral gyrus, L MFG	235	-41	-14	60
Scared < Calm					
None					

ACC = anterior cingulate cortex, BG = basal ganglia, CG = cingulate gyrus, FG = fusiform gyrus, IFG = inferior frontal gyrus, IOG = inferior occipital gyrus, IPL = inferior parietal lobule, L = left, LG = lingual gyrus, MeFG = medial frontal gyrus, MFG = middle frontal gyrus, MOG = middle occipital gyrus, MTG = middle temporal gyrus, PCC = posterior cingulate cortex, PG = parahippocampal gyrus, R = right, SFG = superior frontal gyrus, SPL = superior parietal lobule, STG = superior temporal gyrus, TG = temporal gyrus.

Table 10. Within-group results for *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	# Voxels	*x*	*y*	*z*
Calm NoGo Brain Activity Within Groups					
FHP					
Happy > Calm					
None					
Happy < Calm					
R SFG	R MFG, R IFG, R MeFG	1011	29	68	3
R IFG	R STG, R MTG	457	50	20	-4
L MFG	L SFG, L ACC	387	-35	62	3
R IPL	R STG	222	50	-44	51
L IFG	L STG, L insula	217	-47	23	-13
FHN					
Happy > Calm					
L Postcentral Gyrus	L precentral gyrus, L STG, L insula, L IPL L MFG	325	-32	-41	60
Happy < Calm					
L OFC	L MFG, L SFG, L IFG, L putamen, L ACC L insula, L NAcc	448	-11	50	-19
L ACC	R ACC	334	-2	26	30
FHP					
Scared > Calm					
None					
Scared < Calm					
R SFG	L SFG, MeFG, MFG, ACC, R IFG	1342	29	68	3
R MFG	R STG, R insula, R IFG	443	29	32	-13
R IPL	R MTG, R postcentral gyrus	310	53	-56	48
R thalamus	ACC, caudate	272	2	-2	12
FHN					
Scared > Calm					
R cuneus	R LG, R FG, R MOG	249	17	-101	12
Scared < Calm					
R SPL	cuneus, precuneus	282	5	-71	60

ACC = anterior cingulate cortex, FG = fusiform gyrus, IFG = inferior frontal gyrus, IPL = inferior parietal lobule, L = left, LG = lingual gyrus, MeFG = medial frontal gyrus, MFG = middle frontal gyrus, MOG = middle occipital gyrus, MTG = middle temporal gyrus, NAcc = nucleus accumbens, OFC = orbitofrontal cortex, R = right, SFG = superior frontal gyrus, SPL = superior parietal lobule, STG = superior temporal gyrus.

Table 11. 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	# Voxels	*x*	*y*	*z*
FHP vs. FHN					
Go					
Happy > Calm					
None					
Happy < Calm					
L STG	L insula, L postcentral gyrus	40	-59	-26	15
L STG		31	-56	8	-10
Go					
Scared > Calm					
None					
Scared < Calm					
None					
Calm NoGo					
Happy > Calm					
None					
Happy < Calm					
R SFG	R MFG	111	20	50	45
R SFG		18	29	68	3
NoGo					
Scared > Calm					
None					
Scared < Calm					
R caudate	L caudate	43	2	2	12
R SFG		32	20	50	45
L MFG	L IFG	24	-47	41	18
R PG		21	20	-20	-28
L MFG		20	-38	35	42
R IPL	R MTG	18	50	-68	33
R SFG		18	2	29	48

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 12. Ratings of Valence and Arousal for Faces on the Emotional Go-NoGo Task. Means and standard deviations unless otherwise noted.

	FHP	FHN
N	19	17
Valence[a]		
Happy	6.43(1.26)	6.08(.89)
Scared	4.64(1.14)	4.52(.79)
Calm	4.58(1.36)	4.47(.70)
Arousal[b]		
Happy	4.29(1.6)	3.95(1.71)
Scared	4.71(1.91)	4.64(1.63)
Calm	2.61(1.32)	2.85(1.41)

[a]Scale of 1-9; 1 = Unhappy, 9 = Happy
[b]Scale of 1-9; 1 = Bored/Calm, 9 = Excited/Nervous

There was a main effect of Emotion for both valence and arousal ($F_{2,68}$ = 37.22, *MSE* = 0.94, p = 0.00, partial η^2 = 0.52 ;$F_{2,68}$ = 29.97, *MSE* = 1.2, p = 0.00, partial η^2 = 0.47), but no main effect of Group and no interaction for either measure.

Table 13. Participant Demographics for Youth with Valid Resting State Functional Connectivity Data. Means and standard deviations unless otherwise noted.

	FHP	FHN	Statistic	*p* value
N	16	18		
Age	15.02(1.31)	14.85(1.19)	$t_{32} = .41$	.68
Gender	8F/8M	7F/11M	$X^2_1 = .42$	.52
Caucasian (%)	81.25	77.78	$X^2_1 = .06$	.80
IQ[a]	112.31(8.3)	111.78(10.59)	$t_{32} = .16$	.87
SES[b]	31.2(13.13)	27.17(13.45)	$t_{32} = .88$	.39
PDS[c] Crockett Stage	3.81(1.11)	3.56(.71)	$U_{32} = 108.5$ $Z = 1.33$	.22
Tanner Stage	4.0(1.21)	4.17(.71)	$U_{32} = 142.5$ $Z = .06$	.96

[a]Wechsler Abbreviate Scale of Intelligence
[b]Hollingshead Index of Social Position
[c]Pubertal Developmental Scale

Table 14. Participant Personality Characteristics for Youth with Valid Resting State Functional Connectivity Data. Means and standard deviations unless otherwise noted.

	FHP	FHN
N	16	18
CDI[a] T-score	43.06(5.69)	41.83(6.37)
Perceived Stress Scale	33.0(5.77)	33.17(6.61)
UPPS-P-R-C[b] Scale Total	2.78(.37)	2.95(.32)
ICU[c]-Youth Total	18.75(5.12)	16.83(8.31)
ICU-Parent Total	21.69(9.62)	16.28(5.46)

[a]Children's Depression Inventory
[b]UPPS-P Impulsive Behavior Scale for Children; lower values indicate greater impulsivity.
[c]Inventory of Callous-Unemotional Traits

No statisticall significant Group effect for the MANOVA ($F_{5,28}$ = 0.82, p = 0.54, partial η^2 = 0.13) examining these variables.

Table 15. Family History Density of Alcohol Use Disorders, Mood Disorders, and Antisocial Personality Disorder for Youth with Valid Resting State Functional Connectivity Data. Means and standard deviations unless otherwise noted.

	FHP	FHN	Statistic	*p* value
N	16	18		
Family History AUD[a]	0.56(.19)	0		
Family History MDD[b]	0.29(.32)	0.14(.25)	U_{32} = 92, Z = 1.96	.08
Family History GAD[c]	0.07(.20)	0.10(.19)	U_{32} = 132.5, Z = .60	.70
Family History SIMD[d]	0.08(.15)	0		
Family History ASPD[e]	0.08(.17)	0.005(.02)	U_{32} = 114.5, Z = 1.65	.31
Family History Mood Composite[f]	0.37(.42)	0.18(.25)	U_{32} = 95.5, Z = 1.76	.10

[a]Alcohol Use Disorder
[b]Major Depressive Disorder
[c]Generalized Anxiety Disorder
[d]Substance Induced Mood Disorder
[e]Antisocial Personality Disorder
[f]Mean Scores of Major Depressive Disorder, Generalized Anxiety Disorder, and Substance Induced Mood Disorder (relatives with co-morbid mood disorders are not weighted more heavily); 3 FHP and 2 FHN youth had relatives with co-morbid mood disorders.

Table 16. Head Movement for Youth with Valid Resting State Functional Connectivity Data. Means and standard deviations unless otherwise noted.

	FHP	FHN	Statistic	*p* value
N	16	18		
Percent Frames Removed	13.71(11.11)	11.85(9.78)	$t_{32} = .52$	.61
Mean DVAR[a] Remaining Mean	5.93(.69)	6.06(.52)	$t_{32} = .64$	.53
FD[b] Remaining Mean	0.11(.03)	0.12(.04)	$t_{32} = .53$	.60

[a]Variation in Normalized Signal Intensity
[b]Frame-to-Frame Displacement

Table 17. Group Differences in Resting State Amygdalar Functional Connectivity Between Left and Right Amygdala and a Priori Hypothesized ROIs in FHP vs. FHN Youth

A. Fisher's *Z* Transformed Between-Group Differences

	dACC	L DLPFC	R DLPFC	L IPL	R IPL
L AMYG	0.42	-1.57	-0.40	-1.29	-0.79
R AMYG	0.11	-0.74	-0.24	-0.24	-0.92

B. *p* values of Between-Group Differences

	dACC	L DLPFC	R DLPFC	L IPL	R IPL
L AMYG	0.67	0.12	0.69	0.20	0.43
R AMYG	0.91	0.46	0.81	0.81	0.36

FDR corrected for multiple comparisons at $p < 0.05$.

AMYG = amygdala
dACC = dorsal anterior cingulate cortex
DLPFC = dorsolateral prefrontal cortex
IPL = inferior parietal lobule
L = left
R = right

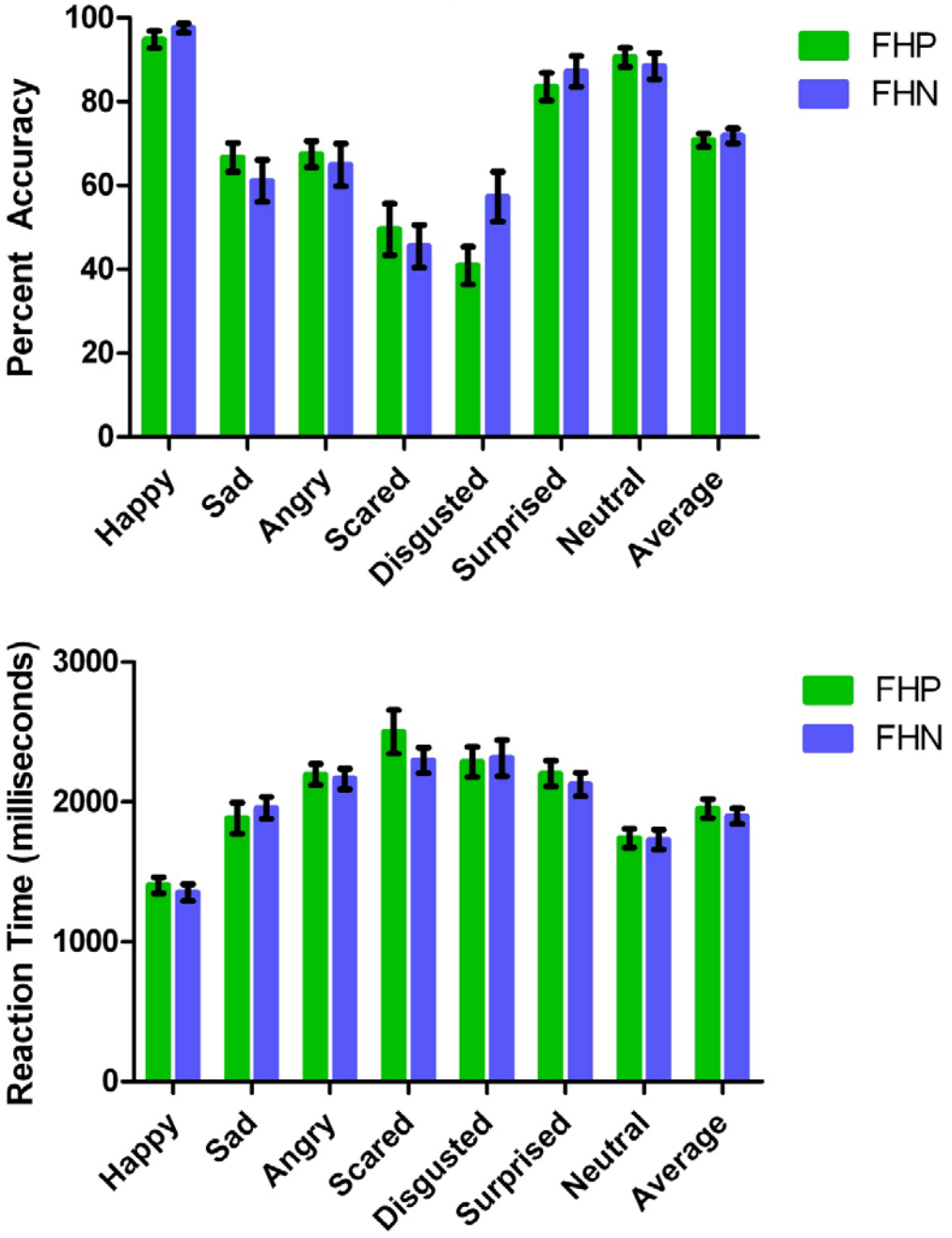
Table 18. Significant Group Differences in Whole-Brain Amygdalar Resting State Functional Connectivity between FHP and FHN Youth.

	FHP	FHN	Number of Voxels	Peak Talairach (x y z)
N	16	18		
L Amygdala				
L SFG	-	+	58	-4 29 53
L Precuneus	-	+	94	-5 -48 34
L SFG/BA8	-	+	87	-20 15 42
L Cerebellum	+	-	53	-20 -58 -45
R Cerebellum	-	+	54	21 -83 -34
R MFG	-	-	88	25 12 45
R Precentral Gyrus	+	-	56	57 -9 24
R Amygdala				
R Cerebellum	+	-	56	30 -68 -18
R MFG	-	+	54	29 8 35
R MTG	-	+	54	45 -27 -8

+ = positive functional connectivity
- = negative functional connectivity

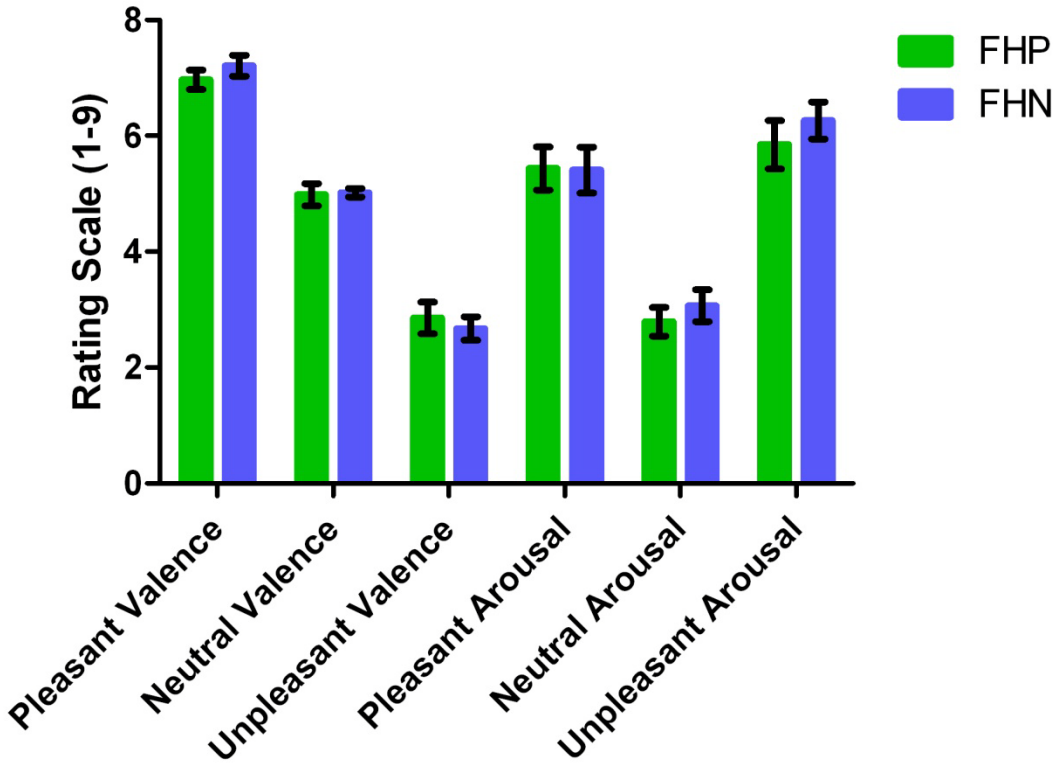
BA = Brodmann area
SFG = superior frontal gyrus
MFG = middle frontal gyrus
MTG = middle temporal gyrus

Figure 7. Emotion Recognition Task Accuracy and Reaction Time.



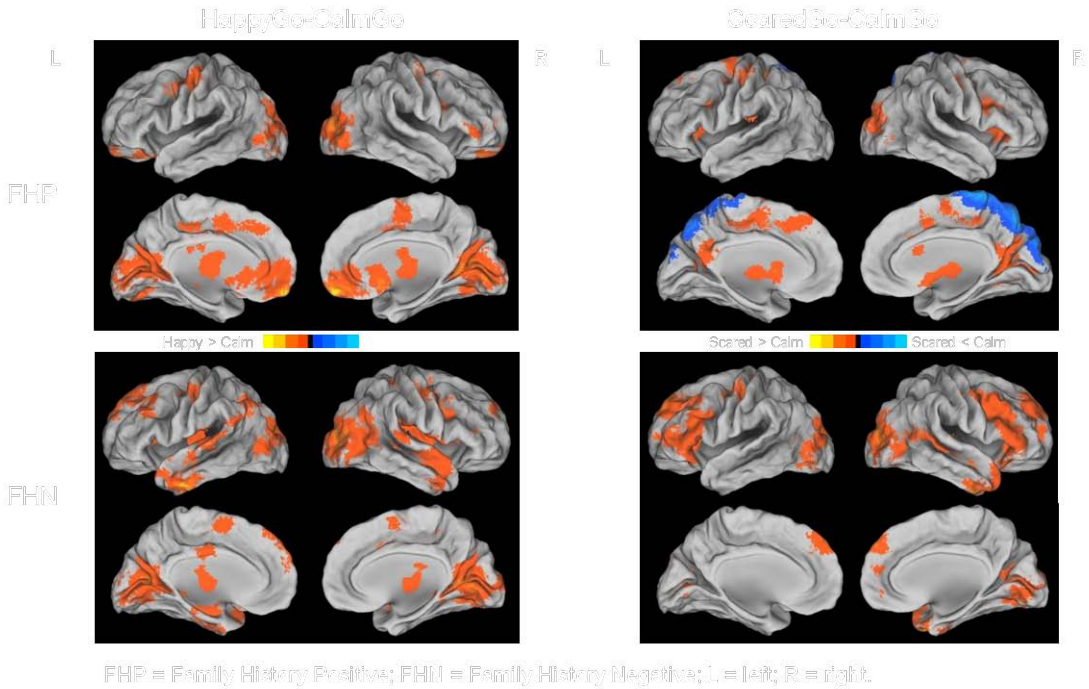
The top panel displays accuracy and the bottom panel displays reaction time for correct trials during the Emotion Recognition Task. There is a significant main effect of Emotion for each of the dependent variables, but no Group or interaction effects.

Figure 8. Affective Rating Task Valence and Arousal Ratings.



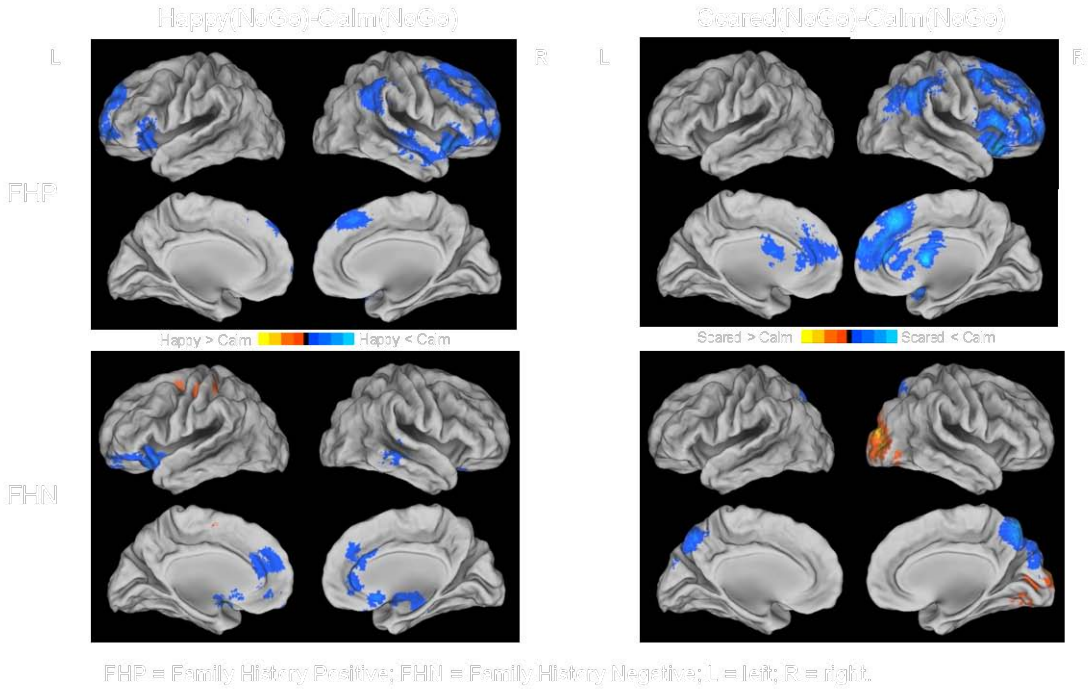
Valence and arousal ratings on a scale of 1-9 are presented for each of the groups on Pleasant, Neutral, and Unpleasant stimuli used in the Affective Rating Task. Significant main effects of Picture type are present for both valence and arousal, but there is no effect of Group or interaction of Group and Picture type.

Figure 9. Neural Reactivity to Emotional Faces in FHP and FHN Youth.



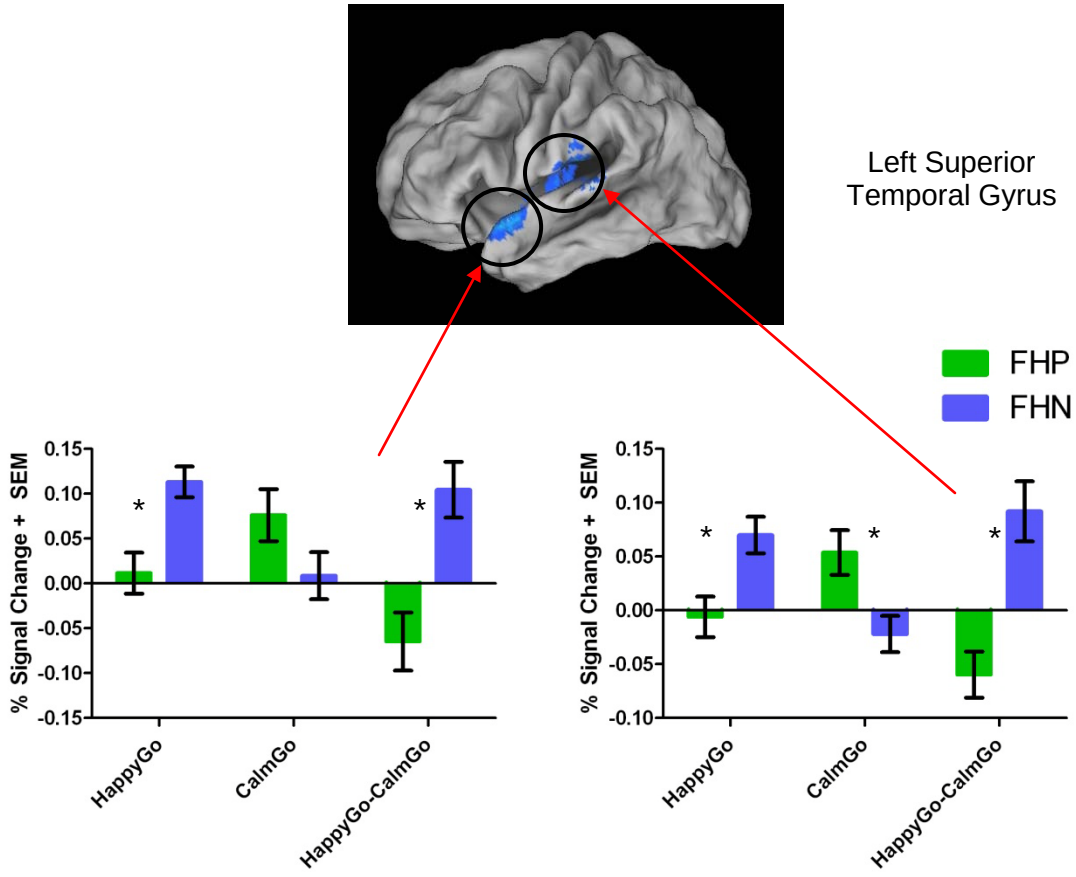
Neural reactivity to both positively valenced (HappyGo-CalmGo) and negatively valenced (ScaredGo-CalmGo) faces is shown for FHP and FHN youth. Increased brain response to positively and negatively valenced faces is shown in warm colors, while decreased brain activity to negatively valenced faces (present in FHP youth) is shown in cool colors. Multiple comparison corrected, ($p/\alpha < 0.05$, ≥ 205 voxels).

Figure 10. Inhibitory Control Brain Activity in Different Emotional Contexts in FHP and FHN Youth.



Inhibitory control brain activity during positively (Happy(NoGo)-Calm(NoGo)) and negatively valenced (Scared(NoGo)-Calm(NoGo)) emotional contexts is shown for FHP and FHN youth. Increased brain during response inhibition is shown in warm colors, while decreased brain activity during response inhibition is shown in cool colors. Multiple comparison corrected, ($p/\alpha < 0.05$, ≥ 205 voxels).

Figure 11. Differences in Brain Activity to Positively Valenced Faces in FHP vs. FHN Youth.

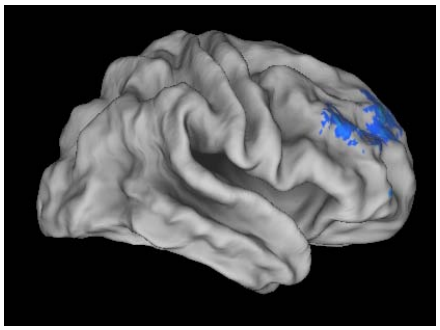


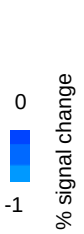
*$p < 0.05$
FHP = family history positive
FHN = family history negative

FHP youth show blunted brain response to Happy vs. Calm faces in two clusters in the left superior temporal cortex compared with their peers. Multiple comparison corrected, ($p/\alpha < 0.01/0.05$).

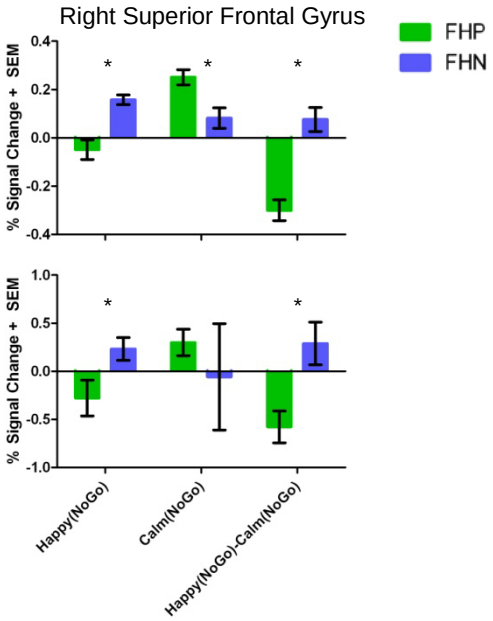
Figure 12. Differences in Inhibitory Control Brain Activity in FHP and FHN Youth.

A. Happy(NoGo)-Calm(NoGo)

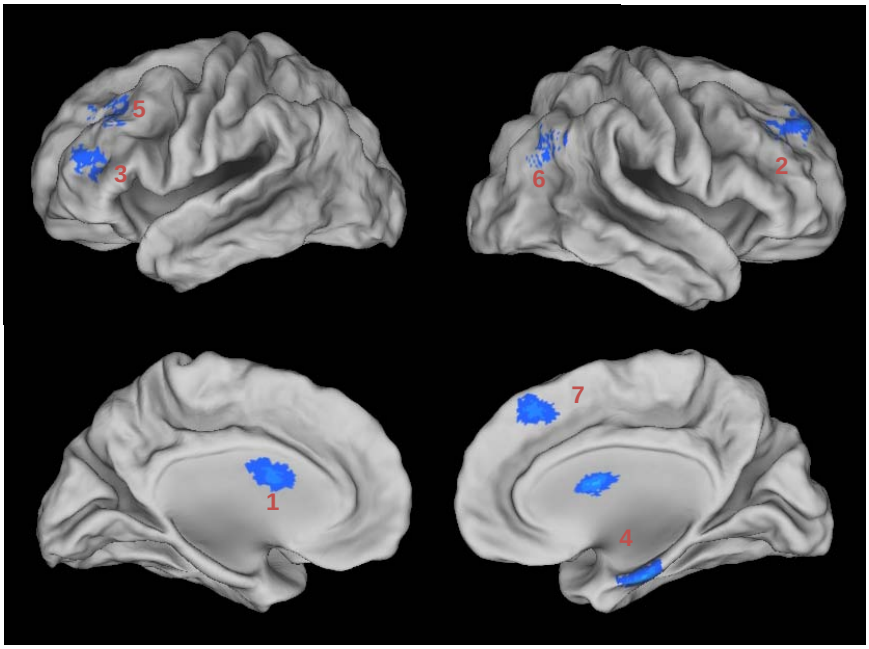




FHP < FHN



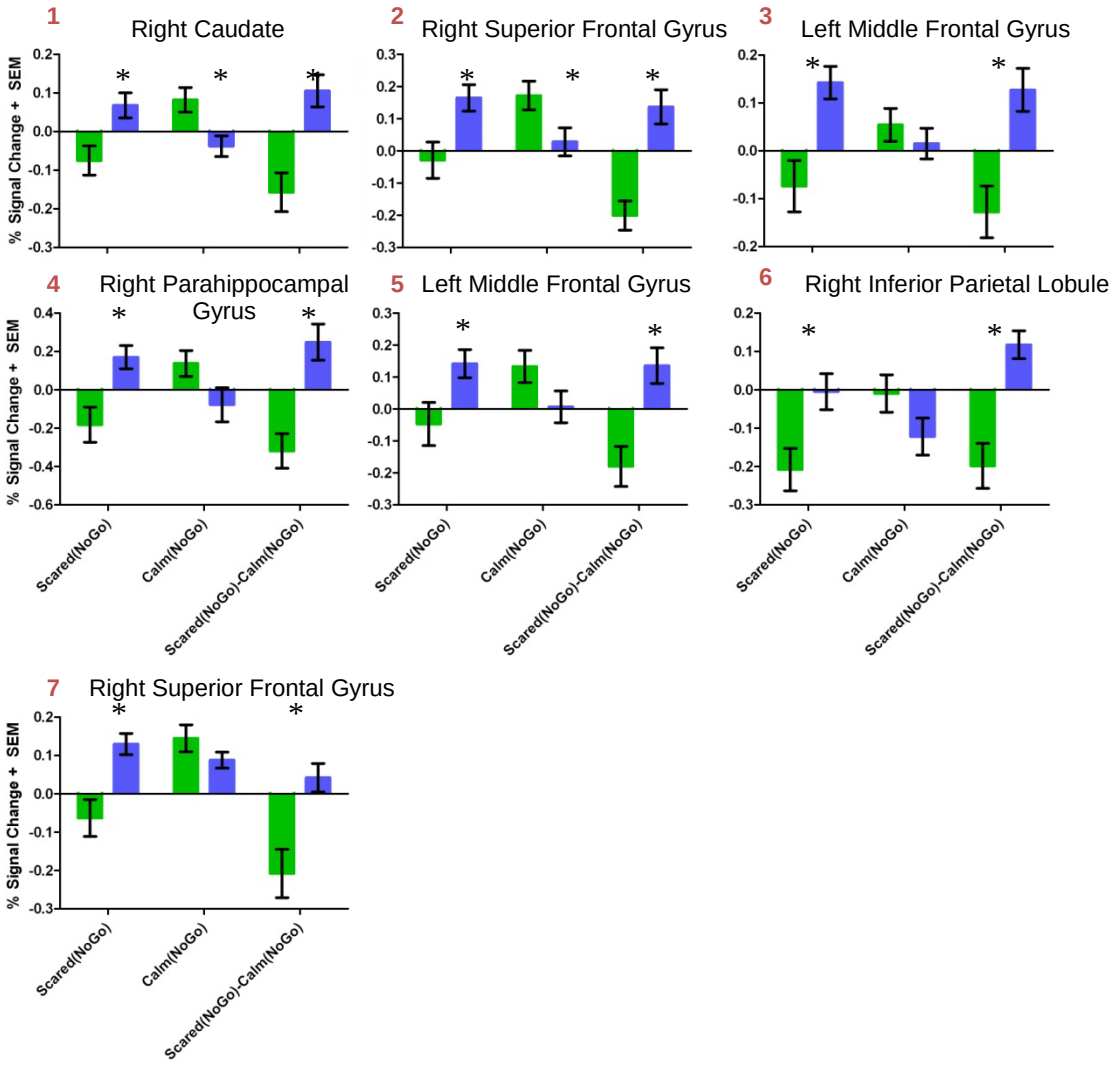
B. Scared(NoGo)-Calm(NoGo)



L

FHP < FHN

R

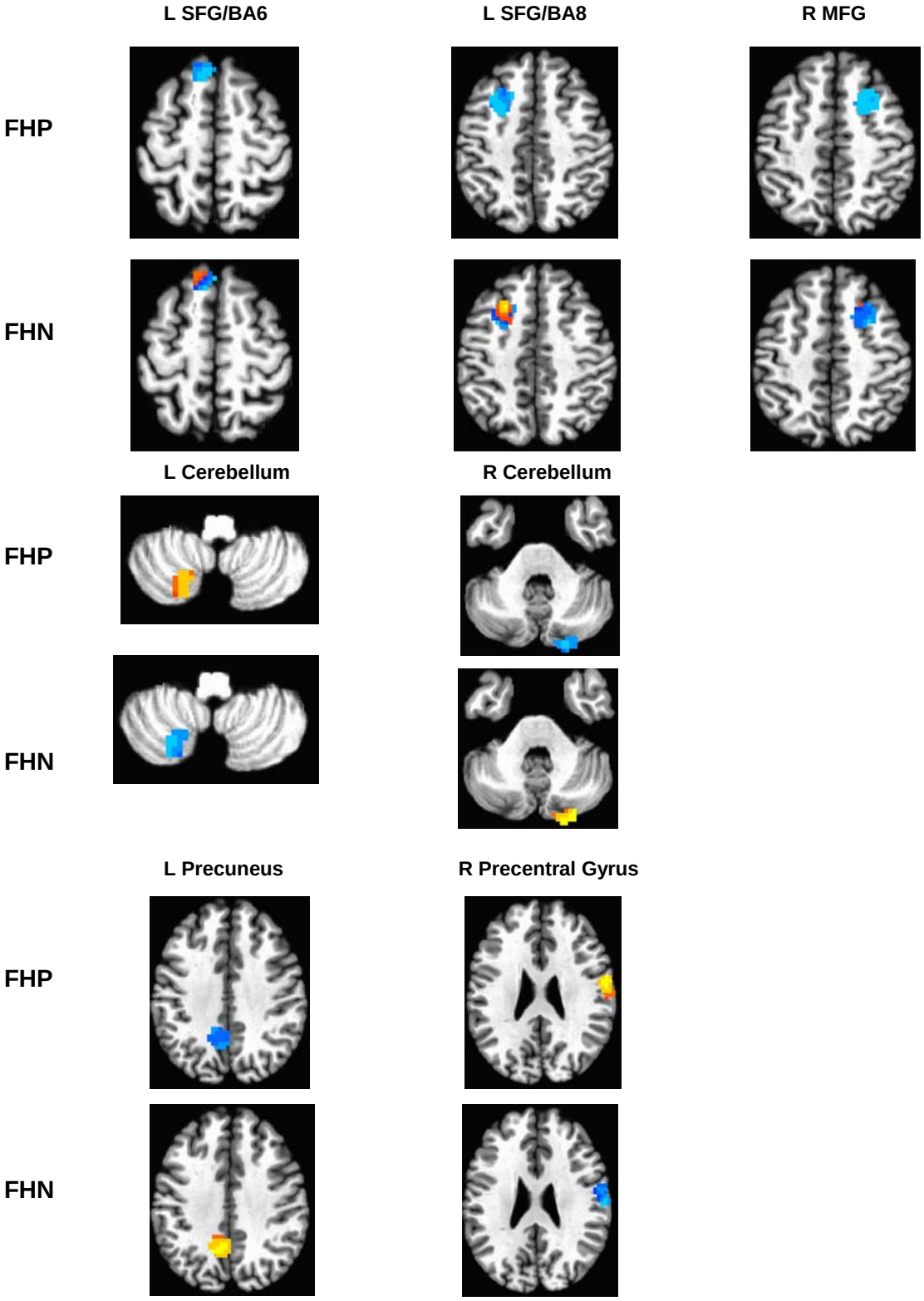


*$p < 0.05$
FHP = family history positive
FHN = family history negative
L = left
R = right

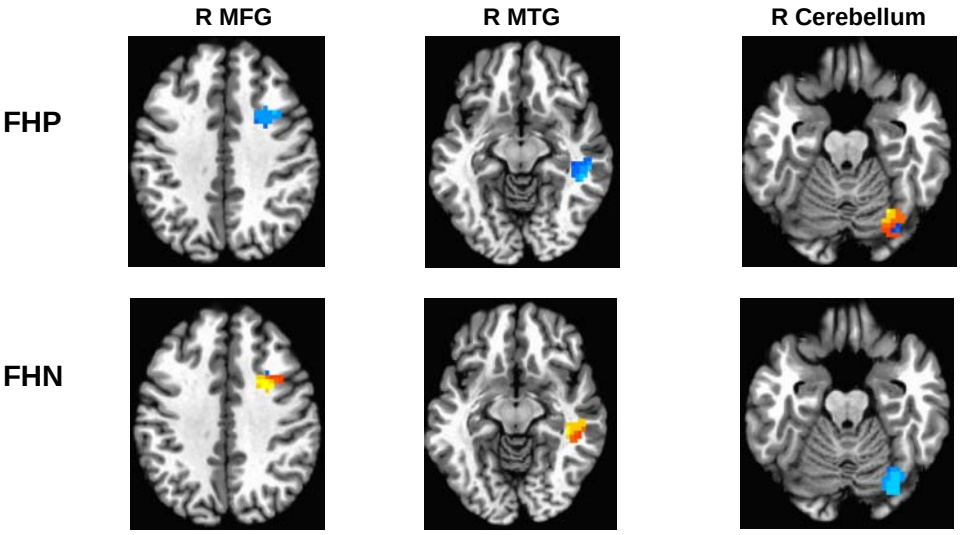
Compared with their peers, FHP youth have weaker cognitive control brain activity during both positively valenced (A) and negatively valenced (B) emotional contexts in frontal, dorsal striatal, and parietal regions, as well as in one cluster of the default mode network (parahippocampal gyrus). Multiple comparison corrected, ($p/\alpha <$ 0.01/0.05).

Figure 13. Amygdalar Resting State Functional Connectivity in FHP and FHN Youth.

A. Left Amygdala



B. Right Amygdala



BA = Brodmann Area
FHP = family history positive
FHN = family history negative
L = left
R = right
Red/Yellow = Positive Functional Connectivity
Blue/Green = Negative Functional Connectivity

FHP youth have significant differences in left and right amygdalar resting state functional connectivity patterns compared with FHN youth. Specifically, most pronounced is weaker functional connectivity between the left amygdala and three clusters in the prefrontal cortex, as well as opposite patterns of functional connectivity with the cerebellum compared with FHN youth. Multiple comparison corrected, ($p < 0.05$, $z \geq 2.25$, ≥ 53 contiguous voxels).

CHAPTER 4. DISCUSSION

4.1 **Summary of Aims and Results**

Over the past 30 years, there has been growing evidence that risk for developing alcoholism is heightened 3-5 fold in individuals with a family history of AUDs (Cotton, 1979; Dawson et al., 1992; Merikangas et al., 1998; Schuckit, 1985). To understand what factors are related to the intergenerational transmission of alcoholism, many researchers have aimed to characterize the behavioral and neurobiological phenotypes that are present in FHP youth, prior to heavy alcohol use. Past studies have identified differences in FHP and FHN youth on neurocognitive measures, including IQ (Ozkaragoz et al., 1997), working memory (Harden and Pihl, 1995), and response inhibition (Nigg et al., 2004), as well as differences in executive functioning brain activity (Cservenka et al., 2012; Cservenka and Nagel, 2012; Mackiewicz Seghete et al., 2013; Schweinsburg et al., 2004; Silveri et al., 2011) and connectivity (Herting et al., 2011; Wetherill et al., 2012). Only a handful of studies have examined emotional processing and brain activity in FHP youth (Heitzeg et al., 2008; Hill et al., 2007a), and none of these included samples with adolescents who were free of heavy alcohol use. Interestingly, alcoholics and FHP individuals have common neural and behavioral features that imply an overlap between emotional processing deficits in these populations (Christensen and Bilenberg, 2000; Glahn et al., 2007; Hill et al., 2001; Marinkovic et al., 2009; Townshend and Duka, 2003; Wrase et al., 2008). Thus, the aim of this dissertation was to investigate affective processing using both behavioral and neuroimaging techniques in FHP adolescents and compare their phenotypes to FHN youth, in the absence of alcohol abuse.

First, FHP and FHN youth were compared on computerized tasks that assessed emotion recognition and affective ratings to emotional and neutral stimuli. No group differences on emotion recognition accuracy or correct recognition reaction time were found between the groups. FHP youth did not rate their valence or arousal levels to pleasant, unpleasant, or neutral stimuli differently than FHN youth. Second, using fMRI, FHP and FHN youth were compared on brain response to emotional faces and inhibitory control during emotional or non-emotional contexts. While there was no main effect of Group for the MANOVA examining hits, correct rejections, reaction time, and d-prime on the task, FHP and FHN youth did show significant differences in brain response to emotional faces and different patterns of brain activity during cognitive control. This suggests that fMRI may be a useful tool for examining risk markers that may be predictive of future alcohol abuse, since many of these findings also map onto what is reported in alcoholics. Finally, rs-fcMRI was used to examine the intrinsic correlations of brain activity in FHP and FHN youth, in the absence of a task. Rs-fcMRI of the left and right amygdala, a key region in emotional processing, had different patterns of connectivity with other brain regions in FHP vs. FHN youth.

These findings suggest that neuroimaging techniques investigating emotional processing may be valuable tools for detecting neurobiological markers that distinguish at-risk youth from their peers. The findings from this dissertation establish novel contributions to the literature on FHP youth that can aid prevention scientists in developing strategies to reduce the incidence of alcohol abuse in high-risk populations. For example, converging evidence on atypical emotional processing and cognitive control in FHP youth could be used to target offspring of alcoholics in treatment programs and provide them with educational and psychological resources on topics such

as stress or good decision-making skills, if it is known that emotional and executive functioning should be attended to in this population.

4.2 Aim 1: Emotion Recognition and Affective Rating

Previous research in alcoholics has found deficits in facial emotion recognition in current (Foisy et al., 2007b; Philippot et al., 1999; Townshend and Duka, 2003) and long-term abstinent alcoholics (Amenta et al., 2013; Foisy et al., 2005; Kornreich et al., 2001). While some authors have suggested that the deficits observed in these populations may be present prior to the onset of alcohol abuse (Foisy et al., 2005), until this date, no studies had examined this question. While, in the current study there was a trend for an interaction between family history status and emotion on recognition accuracy, lack of a significant effect was not related to low power [$(1 - \beta)$] = 0.898. Rather, the effect size of this interaction (partial η^2 = 0.046) was between a small (partial η^2 = 0.01) and medium (partial η^2 = 0.06) effect. Since power was adequate, there may be other factors that limited the detection of any significant group effects or interactions on accuracy during this task, or alternately the effect may not be present in the absence of heavy alcohol use, which could also result in a lack of group differences for accuracy.

Prior research has suggested that emotion decoding deficits may be related to the greater incidence of interpersonal problems in adults with AUDs (Thoma et al., 2013). It is possible that heavy alcohol use may impair alcoholics' ability to interpret emotional expressions, which could negatively impact their everyday social interactions. Studies of alcoholics indicate structural and functional alterations in limbic and cortical regions important for emotional processing, including the amygdala (Durazzo et al., 2011; Fein et al., 2006; Makris et al., 2008; Marinkovic et al., 2009; Wrase et al., 2008), subgenual ACC (Salloum et al., 2007), and prefrontal cortical areas (De Bellis et al., 2005; Fein et al., 2002; Makris et al., 2008; Pfefferbaum et al., 1997), which may be

associated with the deficits in emotional processing abilities. Interestingly, the stability of the emotion recognition deficits observed in alcoholics even after long-term abstinence (Amenta et al., 2013; Foisy et al., 2005), has raised the question of whether pre-existing emotion decoding problems may be a risk factor for future use. The existence of interpersonal problems in offspring of alcoholics (Tarter and Edwards, 1988), suggests that perhaps both risk for alcohol abuse and alcohol itself may be related to emotional processing difficulties, but it is uncertain how each of these factors contribute to the deficits seen in adult alcoholics.

The lack of emotion recognition differences in the current dissertation may be related to the particular outcome variables being measured. For example, while some studies have used similar explicit emotion recognition paradigms (Fernandez-Serrano et al., 2010; Frigerio et al., 2002; Townshend and Duka, 2003), others have used tasks in which alcoholics were required to rate the intensity of the emotions displayed in faces (Foisy et al., 2007a; Kornreich et al., 2001). In these tasks, alcoholics most often overestimated the intensity of the emotions displayed compared to controls, but this overestimation was found to subside with abstinence (Kornreich et al., 2001). Thus, normalization of intensity ratings with abstinence suggests that the neurotoxic effects of alcohol on emotional processing may be a significant contributor to the deficits seen, but it is uncertain how familial history of alcoholism may have contributed to performance on these tasks. Furthermore, since this is the first time this type of emotion recognition paradigm has been used in FHP youth, it is also possible that effects are harder to detect in this age range, since emotional maturation is still underway, which could result in greater heterogeneity in emotion recognition skills than that seen in adulthood.

FHP youth also did not differ from their peers in the time it took to accurately identify the emotion in faces. While our lab has previously found slowed reaction time in

FHP youth on various cognitive tasks (Cservenka et al., 2012; Herting et al., 2010), this may not have translated to an emotional processing task. However, a previous study suggested that alcoholics take more time to decode emotional expressions compared with their peers, and this effect was shown to be specific to emotional decoding tasks, and not observed in control conditions (Foisy et al., 2007b). Also, while stimulus exposure could affect reaction time in alcoholics, the time of face exposure did not affect response time on emotion expression decoding (Foisy et al., 2007b). Thus, it is uncertain whether shorter (< 2 seconds) facial expression displays would have resulted in the emergence of behavioral differences between the groups.

Future work on emotion recognition abilities will need to examine whether the observed interpersonal difficulties in FHP individuals (Jones and Houts, 1992; Sher, 1991; Tarter and Edwards, 1988) are related to emotional processing deficits not tested in the paradigm used in the current study. For example, it is possible that differences in FHP and FHN youth may emerge in response to non-facial stimuli, such as emotional words, since FHP youth have shown different patterns of brain activity to emotional word stimuli than their peers (Heitzeg et al., 2008). In addition, while the current task used the six basic emotional expressions and a neutral face, other emotional processing tasks have incorporated more complex and subtle emotional displays, such as shame or contempt (Kornreich et al., 2001; Philippot et al., 1999), suggesting that future studies may detect group differences in task performance by increasing task difficulty. Given some of the caveats associated with the current task, future studies should continue to clarify this relationship.

The second behavioral task used in the first aim of the current study was the Affective Rating Task, in which participants were instructed to rate the valence and arousal of pictures selected from the IAPS. There were no main effects of Group or

interactions for the valence or arousal scores on this task. Both groups of youth had valence and arousal ratings in the expected ranges for the pleasant, unpleasant, and neutral pictures. Valence was highest for the pleasant pictures and lowest for the unpleasant, while arousal was high for both pleasant and unpleasant, but low for neutral pictures. Although previous studies have suggested that both alcoholics and FHP adults display blunted emotional arousal, there have been mixed findings, since some substance-dependent individuals show heightened arousal to emotional images from the IAPS (Verdejo-Garcia et al., 2006), while alcoholics have been reported to have greater neural activity to negative IAPS pictures than controls (Gilman and Hommer, 2008). Thus, it is possible that blunted arousal in this population may only be present in specific testing conditions or paradigms.

Alternatively, reduced emotional reactivity has been associated with alcoholics with co-morbid antisocial personality disorder. For example, the magnitude of emotion-modulated startle reflex is not affected by the valence of emotional pictures in adults with co-morbid alcoholism and ASPD, while it is affected in alcoholics (Miranda et al., 2003). Despite these previously reported physiological differences, subjective ratings of the emotional pictures did not differ across the groups.

Other research has found that individuals who have had serious problems with alcohol show greater dissociations between physiological arousal (as measured by heart rate variability) and subjective ratings of arousal compared to those with low alcohol problems (Buckman et al., 2010). Additionally, while blunted emotional arousal in FHP adults has been associated with self-reported negative affect, differences in subjective ratings of emotional pictures between FHP and FHN groups were not found (Miranda et al., 2002). These studies suggest that ratings in the current task may not correspond to other emotional arousal measures in high-risk youth. Thus, future work in FHP

adolescents is needed to assess emotional responses to pictures using physiological measures, such as startle reflex and cortisol responses, both of which have been shown to be blunted in individuals with family history of alcoholism (Miranda et al., 2002; Moss et al., 1999; Sorocco et al., 2006).

4.3 **Aim 2: Functional Magnetic Resonance Imaging**

The second aim of this dissertation examined neural responses associated with reactivity to emotional faces and inhibitory control using fMRI. The results indicated that despite no differences in amygdalar reactivity to emotional faces in FHP youth compared with their peers, the two groups showed whole-brain differences in brain response to happy faces, but not scared faces. Furthermore, whole-brain analysis also indicated that FHP youth had reduced brain activity in brain regions that have been implicated in cognitive control, including frontal and parietal areas when inhibitory control was examined in the positively and negatively valenced emotional contexts. Importantly, these differences were seen despite no significant group effects or interactions on performance, including hits, correct rejections, reaction time, or d-prime during the task. These findings could suggest that FHP youth show signs of blunted response to emotional stimuli and reduced cognitive control in emotional contexts at the neural level, which may reflect a combination of genetic and environmental markers associated with family history risk related brain response. The presence of these neural differences in the absence of alcohol-induced neurotoxicity could aid in the identification of early markers that could be predictive of future maladaptive behavior.

4.3.1 *Neural Reactivity to Emotional Faces*

Surprisingly, the ROI analysis of the amygdala indicated that FHP youth did not show differences in neural response to either scared or happy faces compared with their peers. This lack of a significant finding may be due to various population and task-

related factors. For example, previous research examining amygdalar reactivity to emotional faces in FHP adults had a different task design (emotion matching) and control conditions (geometric shapes) than in the current study (Glahn et al., 2007). A calm face was chosen as the control face for this dissertation due to the evidence for emotional reactivity to neutral faces in developmental populations (Thomas et al., 2001b). Thus, the type of control stimulus used is one of the differences between the current and previous studies. Furthermore, the findings in FHP adults and alcoholics may reflect a direct influence of alcohol use on amygdalar reactivity, since in these studies even FHP adults had multiple experiences with heavy episodes of alcohol use. Given evidence of structural alterations in the amygdala due to alcohol in animal models (Alvarez et al., 1989; Koss et al., 2012) and human studies (Durazzo et al., 2011; Fein et al., 2006; Makris et al., 2008; Wrase et al., 2008), it is plausible that reactivity of this region may change largely as a result of alcohol neurotoxicity. Additionally, there are differences across studies in how the amygdala is defined for ROI analyses. For example, in the current study, an automated segmentation was used that defined the amygdala based on grey and white matter boundaries of the anatomy from each participant's T1-weighted structural MRI scan. However, other studies used a coordinate-based approach to define the amygdala, in which spheres are created around a peak coordinate of previously published amygdalar task-related activity (Glahn et al., 2007), or used different software packages for anatomical segmentation (Marinkovic et al., 2009). These methodological variations could result in different findings across studies, since peak amygdalar activation may depend on the age of study participants, while different software packages could affect the delineation of amygdalar boundaries.

Despite lack of ROI group differences, FHP youth did show significantly reduced brain activity to happy faces compared with their peers in two clusters located in the left superior temporal gyrus. The superior temporal cortex has been consistently implicated in face perception during fMRI tasks (Fusar-Poli et al., 2009; Haxby et al., 2000; Narumoto et al., 2001). Blunted activity in this region in FHP youth is interesting given evidence of reduced activity in this region during emotion discrimination in individuals with high levels of social anhedonia (Germine et al., 2011). Reduced reactivity to positive emotional faces could explain socio-emotional and interpersonal difficulties previously reported in alcoholics, such that the current findings suggest possible pre-morbid risk factors for social-emotional problems in FHP youth.

4.3.2 *Cognitive Control During Emotional Contexts*

One of the most robust findings of the fMRI aim supported the hypothesis that FHP youth would show reduced brain activity during inhibitory control in runs with target emotional faces compared with their peers. Specifically, FHP youth displayed widespread fronto-parietal deactivation during response inhibition in both the positive and negative emotional contexts. These findings are the first to show inhibitory control brain activity differences between FHP and FHN youth in an Emotional Go-NoGo task, and support previous studies that have reported reduced executive function brain activity in FHP adolescents during fMRI tasks (Cservenka et al., 2012; Cservenka and Nagel, 2012; Mackiewicz Seghete et al., 2013; Schweinsburg et al., 2004). Further, these results indicate that when cognitive control is required in the presence of pre-potent responses that are initiated towards emotional stimuli, reduced executive functioning brain activity is pronounced despite lack of behavioral differences between the groups. Interestingly, while there were no differences in brain activity to scared faces between FHP and FHN youth, inhibitory control deactivation in the frontal lobe during the

negatively valenced emotional context was even more widespread than when positively valenced target faces were present. This suggests that despite no significant differences in brain activity to scared faces in FHP and FHN youth, the impact of these target faces on executive control can still be observed. In the majority of the frontal lobe areas (SFG and MFG, as well as some of the IFG) in which FHP youth showed deactivation during response inhibition, the effect was driven by group differences in brain response to NoGo faces during the emotional context as opposed to the emotionally neutral run of the task. These findings add to a growing literature on frontal executive dysfunction in FHP youth. Weaker inhibitory control activity on a traditional Go-NoGo task has been observed in FHP adolescents, also in the presence of comparable task performance between the at-risk and control groups (Schweinsburg et al., 2004). Additionally, our lab has found frontal lobe deactivation during verbal (Cservenka et al., 2012) and spatial working memory tasks (Mackiewicz Seghete et al., 2013), as well as decision-making (Cservenka and Nagel, 2012) in FHP youth. Thus, the current findings suggest that these results translate to cognitive control in emotional contexts as well.

Another area of group differences in BOLD response was seen in the caudate nucleus, a region known to be involved in inhibitory control (Menon et al., 2001; Rubia et al., 2006). FHP youth showed reduced activity during NoGo trials when negatively valenced target faces were present compared to their peers, suggesting reduced inhibitory control in the face of aversive stimuli. Interestingly, they showed positive activation in this region when inhibition took place in the non-emotional 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.

FHP youth also showed greater deactivation during cognitive control in the right parahippocampal gyrus, a region associated with the DMN (Andrews-Hanna et al., 2010; Fox et al., 2005; Greicius et al., 2003; Ward et al., 2013), which typically shows reduced activation during cognitively demanding tasks (McKiernan et al., 2003; Thomason et al., 2008). This finding is interesting and may suggest that FHP youth need to suppress DMN activity to a greater extent than their peers in order to maintain a high level of task performance. Thus, this may be a compensatory brain response in FHP youth due to their reduced efficiency of frontal lobe activation. Greater suppression of DMN activity during task performance could allow the at-risk group to perform on-par with the FHN youth. This could be possible due to potential differences in network organization between FHP youth and their peers. While speculative, in addition to the deactivation of the parahippocampal gyrus, it is likely FHP youth are recruiting additional brain regions during the task that were subthreshold to the statistical correction applied in the current study.

The observation that there was no main effect of group or interaction with the MANOVA that examined task behavior is not unexpected. Previous fMRI studies of FHP youth have often found differences in brain activity between the at-risk and control groups, despite lack of performance differences on the fMRI task used in the study (Cservenka and Nagel, 2012; Mackiewicz Seghete et al., 2013; Schweinsburg et al., 2004). This suggests that the patterns of brain activity seen in FHP youth on these tasks cannot be attributed to differences in task performance between at-risk youth and their peers, but may instead represent underlying phenotypes of risk that task behavior may not be sensitive in detecting. Since daily decision-making and cognitive functioning often take place in the face of ongoing emotional processing, it is important to understand the neural response associated with cognitive control during different emotional contexts

that could interfere with cognitive processing. Future work is needed to examine the integrity of cortico-limbic pathways in FHP adolescents compared with their peers to further characterize the relationship of these brain areas.

4.4 Aim 3: Resting State Functional Connectivity

The third aim of this dissertation used rs-fcMRI to investigate the intrinsic functional connectivity of the amygdala in FHP youth. While results of the *a priori* analysis did not show any significant between-group differences, the secondary whole-brain approach showed reduced functional connectivity between the amygdala and other regions of the PFC (four ROIs), including SFG and MFG. Additionally, FHP adolescents showed atypical connectivity patterns with three clusters in the cerebellum, one in the MTG, one in the precentral gyrus, and one in the precuneus.

In all four prefrontal cortical areas of amygdalar connectivity, FHP youth had significantly reduced spontaneous correlations with the SFG and MFG compared with their peers. The amygdala and PFC have reciprocal connections in the brain, with the most dense connections between the amygdala and medial, as well orbitofrontal, areas (Ghashghaei et al., 2007). However, studies of efferent amygdalar projections in primates suggest that labeling of axon terminals is still present in more dorsal regions of the PFC, although it is comparatively lower (Ghashghaei et al., 2007; Salzman and Fusi, 2010). However, Pessoa (2008) points out, emotion and cognition have often been found to be integrated in more dorsal and lateral regions of the PFC in human fMRI studies during tasks that involve both emotional and cognitive stimuli. Thus, based on this evidence, resting functional connectivity of BOLD response in these regions is plausible. The regulatory role of prefrontal cortical areas in cognition is well established (Luna et al., 2001; Rubia et al., 2006; Tamm et al., 2002; Wagner et al., 2001), suggesting that the current findings may indicate a reduced capacity between PFC

control over limbic structures, such as the amygdala, in at-risk youth. While a few studies have examined amygdalar rs-fcMRI in healthy populations (Kim et al., 2011; Roy et al., 2009), there is even more sparse literature investigating functional connections of the amygdala during development. Recently, Qin et al. (2012) reported that healthy children show reduced integration of resting state connectivity between the amygdala and various brain networks, including prefrontal and association cortices compared with adults. Further, the amygdala's functional connections were absent or slightly negatively connected with the PFC, while there was a positive association between these regions in adults. Thus, it is possible 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 the Qin study, Roy et al. (2009) and Kim et al. (2011) have reported negative functional connections between the amygdala and dorsal PFC, albeit these studies were conducted in adults. While there is certainly evidence for the existence of anti-correlated resting state networks (Chai et al., 2012; Fox et al., 2009) despite arguments that these negative functional connections are artificially introduced due to global signal regression (Murphy et al., 2009), the particular relationship of amygdalar connectivity with these networks remains unclear.

Examination of the association between resting state amygdalar connectivity and behavior may help to clarify the meaning of negative connectivity between the amygdala and the prefrontal cortical seeds in FHP youth. Based on evidence that these regions may be important for emotion-cognition interactions (Pessoa, 2008), correct rejections from each run of the Emotional Go-NoGo task were correlated with each participant's amygdala-PFC correlation coefficient in the four ROIs that showed group differences in connectivity. This analysis indicated that in the left SFG, greater connectivity with

amygdala was significantly related to fewer inhibitory commission errors during the Emotional Go-NoGo task (most significantly during the presentation of positively valenced target faces). This relationship was only present in the FHP group, suggesting that the anti-correlated 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. To confirm this relationship, a correlation analysis showed a significant association between correct rejections and functional connectivity of the left amygdala with the left SFG in FHP youth.

One of the most unique patterns of connectivity was observed in the cerebellum, where FHP youth not only showed significant differences from their peers, but displayed opposite functional connections. For example, FHP adolescents had positive ipsilateral connectivity between the left amygdala and left cerebellum, and negative connectivity between the left amygdala and right cerebellum, both opposite from the patterns seen in FHN adolescents. This pattern of left amygdalar connectivity could represent greater intra- rather than interhemispheric communication between these regions. Interestingly, studies in alcoholics and FHP youth have found other brain areas that also show atypical functional connections with the cerebellum, including reduced fronto-cerebellar connectivity in alcoholics and FHP youth (Herting et al., 2011; Rogers et al., 2012), and atypical resting synchrony of the hippocampus and cerebellum (Pitel et al., 2012). The cerebellum, while classically implicated in motor control (Ito, 2006), has been associated with emotional processing (Schutter and van Honk, 2005; Snider and Maiti, 1976). Animal studies suggest neuronal projections from cerebellar lobules to amygdalar nuclei, 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 the cerebellar abnormalities in FHP individuals and the risk they represent for alcohol abuse.

4.5 Limitations

While the studies in this dissertation present novel findings in neurobiological markers of risk for alcoholism in FHP youth, there are some limitations that warrant mention. First, FHD of alcoholism did not relate to the behavioral measures examined (on the Emotion Recognition Task or Affective Rating Task) and only related to BOLD response in one region of the whole-brain fMRI analysis. It is possible that there is high individual heterogeneity of the contribution of genetic and environmental factors that contribute to family history risk, which may limit the detection of clear linear associations between density and the dependent measures. While there are certainly specific genetic factors that have been associated with the transmission of familial alcoholism, the influence of environment (i.e. exposure to the alcoholic relative, parental rejection, emotional warmth, family violence) also contributes to risk (Barnow et al., 2002; Jacob et al., 2003; Ritter et al., 2002). This may complicate the relationship between a FHD score and behavioral or brain measures. Further, there was a relatively narrow range of FHD in this participant sample, which is comparable to other samples of FHP youth who have been part of the same ongoing longitudinal study. Further work is needed to increase sample size with a more heterogeneous sample of risk, since greater alcohol-related problems are often associated with higher familial density of alcoholism in multiplex alcohol dependence families (Hill and Yuan, 1999; Stoltenberg et al., 1998).

Second, while the sample size collected in this study is comparable to other samples published on behavioral and neuroimaging measures in familial alcoholism, the sample was not large enough to investigate gender differences that may interact with risk status. This investigation is ultimately needed, as there is evidence for gender

effects on brain structure in familial alcoholism (Silveri et al., 2008) which could contribute to the differences in brain structure and functioning between male and female alcohol abusers (Medina et al., 2008; Squeglia et al., 2011).

Third, while every effort was made to gather family history information from both biological parents of youth, only 4 and 5 participants from the FHP and FHN groups respectively had family history information from both parental interviews. Family history information for each adolescent based on single parent and youth report may be incomplete. Future work with this population will need to examine ways to reduce family burden for study participation to increase compliance for gathering family history information from both parents.

Fourth, it should be noted that sample sizes for both the fMRI and resting state imaging analyses were reduced due to performance and movement criteria, for these aims, respectively. While chi square analyses suggested that performance was comparable to the original larger sample of youth, there was a trend indicating more FHP youth were excluded from the resting state analyses due to excessive head movement. Exclusion of participants due to these factors may have removed variance in the youth of interest from the study. For example, the adolescents excluded may be at greater risk for alcohol-related problems, since they were also the ones with poorer inhibitory control on the Emotional Go-NoGo task, which could be an important behavioral marker of risk. Additionally, marginally more head movement in the FHP group could result in removal of specific phenotypes of interest (e.g. perhaps greater head movement is a subtle marker of other risk factors, such as inattention or impulsive personality). Thus, neuroimaging analyses, which require an adequate number of trials to have sufficient power for modeling the hemodynamic response, and also limited head movement to decrease movement-related artifacts that affect the BOLD signal, may bias

the neurobiological phenotypes being studied in FHP and FHN youth. These factors should be taken into consideration in at-risk studies, as well as those examining psychiatric disorders or clinical populations, where performance and movement may differ between the groups of interest and control populations.

Fifth, many studies of familial alcoholism do not report other types of familial psychiatric disorders that may be present in first or second degree relatives of youth. For this dissertation, at least one biological parent was interviewed about the presence of MDD, GAD, SIMD, and ASPD in the youth's family, since many of these disorders are co-morbid with alcoholism, and it is important to determine whether the effects in the current study were related to familial density of these disorders in the participants. While not statistically significant, FHD of MDD was represented approximately double in FHP youth compared with their peers. Covarying for FHD of MDD suggested that the connectivity of the left amygdala and left precuneus was partially explained by FHD of MDD; however, the group effects remained. These results suggest that while FHD of MDD may be associated with some of the observed group differences in brain activity or connectivity, the overall findings confirm robust family history of alcoholism effects. However, future studies should interpret familial alcoholism effects with caution if other types of familial psychopathology are not thoroughly assessed.

Sixth, there are other variables that may relate to emotional processing measures collected in the current study that could differ by family history status. For example, while past 30-day stress was assessed in the participants, extensive and detailed stress history of youth was unknown. Peer, familial, and relationship stressors could impact emotional processing during childhood and adolescence (Taylor et al., 2006; Vanaelst et al., 2012), and also increase risk for alcohol use (Andersen and Teicher, 2009; Aseltine and Gore, 2000). Future studies should administer more detailed

life stressor measures to better assess whether these differences exist in FHP and FHN youth. Furthermore, the current study did not assess severe forms of stress, such as child neglect or child physical or sexual abuse, which have been shown to have effects on emotional (Colvert et al., 2008; Leist and Dadds, 2009) and cognitive functioning (Spann et al., 2012), and could have differed between high-risk and control youth.

Finally, the results of this dissertation are unable to point to cause-and-effect relationships between risk status and future alcohol abuse. However, the ongoing longitudinal study of the FHP youth included in this dissertation will examine whether the findings at baseline from this study will be predictive of future heavy alcohol use initiation.

4.6 Future Directions

While this study was the first to examine emotional processing and brain activity in FHP youth free of heavy alcohol use, there are many areas of inquiry that future studies will need to examine. For example, future research could examine hormones (estradiol and testosterone) and DNA to further clarify the relationship between biology, genetics, and brain structure or function. The relationship between hormones and reactivity to emotional stimuli in at-risk youth could reveal associations between pubertal development and limbic circuitry not yet characterized in this population. Additionally, previous studies have found specific allelic variations (i.e. GABA, BDNF) that relate to cerebellar brain volume (Hill et al., 2011) and insula activity (Villafuerte et al., 2012) in FHP individuals. However, there are no neuroimaging studies of genetic variation in FHP youth in relation to subcortical structures, such as the amygdala. Thus, more extensive work is needed to investigate specific genetic variants that relate to limbic neurocircuitry. Additionally, this dissertation used behavioral measures, fMRI, and rs-fcMRI to examine emotional processing in FHP youth, but structural analysis was not included. Previous

research has found smaller amygdala volume in a comparable sample size of already drinking FHP adolescents and young adults (Hill et al., 2001), so this analysis should be replicated in the current cohort of FHP youth, who are free of heavy alcohol use. Furthermore, to better characterize the relationship between limbic and cognitive control circuitry, diffusion tensor imaging studies could examine white matter pathways in at-risk youth using an ROI approach to characterize the integrity of the uncinate fasciculus, a tract between the amygdala and PFC, which has been shown to be compromised in alcoholics (Schulte et al., 2012). Given the current fMRI findings showing blunted superior temporal cortex activity to positively valenced faces in FHP youth, future work should inquire whether these results are specific to positive emotional faces or translate to other emotional stimuli in this population. Additionally, it will be important to examine how socio-emotional processing brain regions, such as the temporal lobe differ in functional and/or structural connectivity between FHP and FHN youth. Finally, it will be critical to investigate how the initation of alcohol use impacts emotional processing brain activity and cognitive control in emotional contexts, as well as determine how resting state connectivity between limbic and top-down cognitive control brain regions are affected as a result of alcohol use in at-risk vs. control youth.

4.7 Summary and Conclusions

The goal of this dissertation thesis was to investigate brain function and behavior, related to emotional processing in FHP youth, as well as examine their associations with executive functioning, *prior to heavy alcohol use*. The results of these studies suggest that there was a failure to detect differences in emotion recognition or subjective ratings of affective stimuli between FHP and FHN youth. However, fMRI showed that neural reactivity to emotional faces and cognitive control brain response in emotional contexts were reduced in FHP youth compared to their peers. Specifically, emotional response

was blunted in the superior temporal gyrus, while inhibitory control brain activity was reduced in fronto-striatal brain regions. Further, FHP youth had significant differences from their peers in resting state synchrony between the amygdala, and other brain areas, including the PFC and cerebellum. Additionally, poorer amygdala-PFC functional connectivity in one area of the frontal lobe was related to cognitive control during the Emotional Go-NoGo task in FHP youth.

This dissertation includes the first studies to examine emotion recognition, affective ratings of emotional stimuli, brain response to emotional faces, emotion-cognition interactions, and resting state functional connectivity in FHP youth. The main findings from these studies suggest that even in the absence of any heavy alcohol or substance use, FHP youth have altered limbic brain response to positive affective social stimuli. Additionally, reduced fronto-striatal brain activity during response inhibition in FHP youth compared with their peers suggests that emotional contexts may interfere with executive functioning circuitry to a greater degree in at-risk youth compared with their peers. Finally, even at rest, FHP youth show differences in intrinsic connectivity between the amygdala and other brain regions, especially the PFC and cerebellum, both of which are critical to executive functions. Thus, these findings contribute novel information on emotional processing in FHP adolescents that can aid future research in this population, with the ultimate goal of establishing prevention strategies to reduce the development of AUDs and their burden to the individual and society.

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SUBJECT NUMBER: __ __ __ __ __ - __ __ __ __ DATE: __ __ / __ __ / __ __

During the emotional faces task:

1. How important was it for you to do well?
    1) Not at all
    2) A little
    3) Moderately
    4) Very

2. How difficult was it for you to do well on this task?
    1) Not at all
    2) A little
    3) Moderately
    4) Very

3. How well do you think you did on the task?
    1) Very poorly
    2) Poorly
    3) OK
    4) Well
    5) Very well

4. Did seeing emotional faces cause you to have an emotional reaction?
    1) No
    2) Only for the happy faces
    3) Only for the scared faces
    4) Yes