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Neurobiological Phenotypes Associated with a Family History of Alcoholism

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Abstract

Background—Individuals with a family history of alcoholism are at much greater risk for developing an alcohol use disorder (AUD) than youth or adults without such history. A large body of research suggests that there are premorbid differences in brain structure and function in family history positive (FHP) individuals relative to their family history negative (FHN) peers.

Methods—This review summarizes the existing literature on neurobiological phenotypes present in FHP youth and adults by describing findings across neurophysiological and neuroimaging studies.

Results—Neuroimaging studies have shown FHP individuals differ from their FHN peers in amygdalar, hippocampal, basal ganglia, and cerebellar volume. Both increased and decreased white matter integrity has been reported in FHP individuals compared with FHN controls. Functional magnetic resonance imaging studies have found altered inhibitory control and working memory-related brain response in FHP youth and adults, suggesting neural markers of executive functioning may be related to increased vulnerability for developing AUDs in this population. Additionally, brain activity differences in regions involved in bottom-up reward and emotional processing, such as the nucleus accumbens and amygdala, have been shown in FHP individuals relative to their FHN peers.

Conclusions—It is critical to understand premorbid neural characteristics that could be associated with cognitive, reward-related, or emotional risk factors that increase risk for AUDs in FHP individuals. This information may lead to the development of neurobiologically informed prevention and intervention studies focused on reducing the incidence of AUDs in high-risk youth and adults.

Keywords

family history; alcoholism; EEG; MRI; fMRI; DTI

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1. FAMILY HISTORY OF ALCOHOLISM

It is well established that family history of alcoholism is a significant risk factor for the development of alcohol use disorders (AUDs; Cloninger et al., 1986; Goodwin, 1985; Schuckit et al., 1972). This evidence comes from the observation that alcoholism is prevalent among relatives (Schuckit et al., 1972), and there is a higher concordance of the disorder in both male and female monozygotic twins (Heath et al., 1997), with an estimated 30-50% of individual risk attributed to genetics (Heath et al., 1997; Kaprio et al., 1987; Knopik et al., 2004). Additionally, adoption studies suggest similar risk in individuals living apart from biological parents, which provides further support for the heritability of the disorder (Bohman, 1978; Cloninger et al., 1981; Goodwin et al., 1974). A quarter of youth in the United States have a family history of alcoholism (Grant, 2000), which increases their likelihood of developing an AUD three-to-five fold (Cotton, 1979). Greater density of alcoholism in one's family is also associated with higher risk of developing an AUD (Hill and Yuan, 1999). Furthermore, family history of alcoholism increases the risk of alcohol-related problems among adolescents (Lieb et al., 2002). Given the strong evidence that family history of alcoholism significantly increases AUD risk, it is critical to understand the neurobiological underpinnings that contribute towards the heritability of the disorder. Nonetheless, many individuals with a family history of alcoholism do not go on to develop AUDs (Werner, 1986), so it is equally important to identify neurobiological mechanisms that may confer resilience against heavy alcohol use.

Definitions of family history of alcoholism have varied from parental or nonparental presence of AUDs, examination of maternal and/or paternal sides of the family, uni- or multigenerational presence of the disorder, or quantification of multiple relatives with the disorder (Alterman, 1988). Despite these varying definitions, previous neuroimaging research has largely categorized individuals as having a positive family history of alcoholism (FHP) if they had at least one biological parent or two or more second degree relatives diagnosed with AUDs (e.g., Andrews et al., 2011, Cservenka and Nagel, 2012), while family history negative (FHN) individuals had an absence of familial alcoholism in first (e.g., Heitzeg et al., 2010) or first and second degree relatives (e.g., Cservenka and Nagel 2012; Squeglia et al., 2014). While many studies have conducted group-level analyses using these dichotomous definitions (e.g., Herting et al., 2010; Schweinsburg et al., 2004; Sjoerds et al., 2013), others discussed in this review have used continuous measures, such as a quantitative calculation of degree of family history density (FHD; Alterman, 1988) of AUDs (e.g., Cservenka et al., 2015; Silveri et al., 2011; Spadoni et al., 2008) to examine the extent to which the presence of the disorder across multiple relatives may contribute to degree of risk for developing AUDs. Lastly, another common way family history has been defined is by recruiting participants who are considered high-risk due to multi-generational presence of AUDs within families with multiplex alcohol dependence where the first generation in which AUDs were present included two biological brothers with the disorder (e.g., Hill et al., 2001). For simplicity, FHP and FHN will be used in this review to describe group differences between individuals with and without a family history of alcoholism, except in studies of multiplex alcohol dependence where high-risk (HR) and low-risk (LR) offspring are described as those who do and do not come from families with

multigenerational alcohol dependence, respectively. Finally, FHD will be used to discuss findings where density of familial AUDs was examined with a quantitative continuous variable.

Using the definitions described above, a multitude of studies have examined neurocognitive, behavioral, and personality characteristics in individuals with familial alcoholism. There is growing research on the neural correlates that may underlie some of the characteristics that could increase risk for the development of AUDs as well as markers that could provide resilience against the development of AUDs, especially in young adult and adult samples with minimal heavy alcohol use. This review will summarize the neurocognitive and neurobiological features present in youth and adults with a family history of alcoholism. Early studies using electroencephalography (EEG) and event-related potentials (ERP) identified electrophysiological differences between FHP and FHN individuals, while more recent studies using structural and functional magnetic resonance imaging (fMRI), as well as diffusion tensor imaging (DTI), have reported a variety of volumetric, functional, and white matter microstructure differences between FHP and FHN youth and adults.

2. NEUROCOGNITION AND AFFECT

Neurocognitive studies consistently report that individuals with familial alcoholism have deficits in verbal and language abilities (Drejer et al., 1985; Knop et al., 1985; Tapert and Brown, 2000), visuomotor, visuospatial, and perception skills (Aronson et al., 1985; Garland et al., 1993; Ozkaragoz et al., 1997; Schaeffer et al., 1984; Tarter et al., 1989), and in various domains of executive functioning (Corral et al., 2003; Gierski et al., 2013; Harden and Pihl, 1995; Hesselbrock et al., 1991). For example, compared with FHN individuals, FHP adults had greater preservative errors on the Wisconsin Card Sorting Task (WCST), and slower reaction time during the Trail Making and Arithmetic Switching Tasks, which reflect weaknesses in set-shifting (Gierski et al., 2013). Similar findings were present in FHP children, who also showed more perseverative errors on the WCST compared with their FHN peers (Corral et al., 2003). The authors suggested that this could be reflective of a developmental delay, as FHP children did not exhibit a reduction in perseverative errors on the WCST when assessments were conducted 3.5 years apart, while control youth did show improvements in performance (Corral et al., 2003). Poor planning and abstract problem solving abilities have also been found in multiple studies of FHP individuals (Drejer et al., 1985; Schaeffer et al., 1984; Tarter et al., 1989), which may also be indicative of executive functioning immaturity, thereby leading FHP youth or adults to make poor choices with regards to alcohol use.

Furthermore, on basic tasks of motor inhibition, FHP individuals were more impulsive and had difficulties in response inhibition compared with their FHN peers (Acheson et al., 2011a; Saunders et al., 2008). Inhibitory control problems have also been found on more cognitively demanding tasks, as FHP adults made more errors than FHN individuals when performing the Stroop (Lovallo et al., 2006), which requires the maintenance of attention, conflict monitoring, and response inhibition. Delay discounting paradigms indicate that FHP adults are also less able to delay reward gratification (Acheson et al., 2011b), perhaps reflecting heightened impulsivity, which may contribute to alcohol-related problems. It is

possible that poor decision-making abilities contribute to AUD risk in this population and may vary by sex, since FHP males were reported to be more attentive to financial gains, suggesting a greater propensity for reward-driven behavior compared to FHP females or FHN individuals (Lovallo et al., 2006). These findings also translate to studies of largely alcohol-naïve youth, as poorer response inhibition was present in FHP children and adolescents compared with their FHN peers (Nigg et al., 2004). Thus, a strong body of research points to executive functioning abnormalities, including set-shifting weaknesses and inhibitory control deficits, in FHP individuals in the absence of AUDs. While not all neuropsychological studies have found performance differences between FHP and FHN individuals (Alterman et al., 1989; Bates and Pandina, 1992; Hesselbrock et al., 1985), neuroimaging studies may provide insight into the neurobiological correlates of previously reported abnormalities in cognitive functions in familial alcoholism.

Not only are there top-down cognitive control weaknesses in FHP individuals, but there are also differences in emotional processing and reactivity between FHP adults and their FHN peers, which could be other contributing factors to the emergence of AUDs in this population. Both physiological and subjective affective responses are altered in FHP individuals, as they have shown reduced emotion-modulated startle (Miranda et al., 2002), blunted stress response (Sorocco et al., 2006), and higher rates of internalizing symptoms (West and Prinz, 1987) relative to their FHN peers. Other studies have reported that FHP children experience greater emotional dysregulation and affective problems than their FHN peers (Christensen and Bilenberg, 2000; West and Prinz, 1987). In particular, negative affect in adolescents mediated the relationship between parental history of alcoholism and risk-taking, the latter of which was significantly related to substance use (Ohannessian and Hesselbrock, 2008). These findings suggest that in addition to weaknesses in cognitive control that may lead to maladaptive behaviors in FHP youth and adults, there are also affective pathways that can confer risk for AUDs in this population. Thus, studies examining the neurobiology associated with familial history risk should examine neural markers of risk associated with top-down cognitive control and bottom-up emotion and reward processing, their interaction, and importantly, their ability to predict future escalation of heavy drinking.

3. ELECTROENCEPHALOGRAPHY AND EVENT-RELATED POTENTIALS

Over 30 years ago, the first studies to examine neurobiological correlates of familial risk for alcoholism used EEG and ERP to identify neurophysiological markers of risk for AUDs (Begleiter et al., 1984; Elmasian et al., 1982). Many of these studies have been extensively reviewed by Polich and colleagues (1994), as well as Rangaswamy and Porjesz (2014), but the key findings are described here. The vast majority of these investigations have focused on P3 potentials during the presentation of auditory or visual stimuli. The P3 component is linked with attentional and working memory processes when individuals have to attend to a target stimulus. Initial studies reported lower P3 amplitude in both FHP adult men and FHP boys compared to FHN peers. A meta-analysis by Polich and colleagues (1994) reviewed the mixed evidence regarding the amplitude of the P3 component in familial risk studies, but it appeared that young males show the greatest reduction in amplitude of this component during difficult visual tasks. The authors of this meta-analysis argued that by examining the P3 component, researchers can potentially detect both cognitive dysfunction in those at high

risk for alcoholism, as well as find a neural correlate of vulnerability for developing AUDs that can inform prevention efforts aimed at identifying individuals at highest risk for the disorder (Polich et al., 1994). Furthermore, some of the neural markers that may differentiate FHP vs. FHN individuals appear to also be present at rest, as multiple studies have found that beta power is higher in FHP individuals than their FHN peers during resting EEG (Rangaswamy and Porjesz, 2014).

4. BRAIN VOLUME

With the advent of neuroimaging technology, numerous studies have aimed to understand whether a family history of alcoholism is associated with brain volume alterations that could, in part, explain the higher vulnerability of FHP individuals to develop AUDs. These investigations have primarily used region-of-interest analyses to determine whether gray matter volumes may be atypical in familial alcoholism.

Since reward and emotion-serving brain regions may be one pathway of risk towards AUDs, a number of studies have measured amygdalar volume in FHP and HR individuals (Cservenka et al., 2015; Dager et al., 2015; Hill et al., 2001, 2013c), as reductions in amygdalar volume have been shown in alcoholics (Wrase et al., 2008). Hill and colleagues (2001) were the first to report reduced right amygdalar volume in HR adolescents and young adults relative to LR controls. Both this study and subsequent studies by Hill and colleagues (2007a, 2013a, 2007b, 2013b, 2013c, 2011, 2009), compared brain volume between HR and LR individuals, but included some adolescents and adults with alcohol/substance abuse or dependence, so family history and alcohol use effects cannot be completely dissociated. A subsequent study of amygdalar volume with a larger sample showed reduced volume (bilaterally) – a phenotype that was moderated by genetics (Hill et al., 2013c). HR individuals and carriers of the short “S” allele for the serotonin transporter (5-HTTLPR) gene had smaller amygdalar volume compared to those with the long “L” allele. Since the S allele is associated with vulnerability to stress and risk for alcohol dependence, these findings suggest that genotyping those with familial alcoholism is critical to understanding the interplay of gene x family environment interactions that could contribute to AUD risk. A recent study that examined a number of subcortical brain regions implicated in affect and reward, found reduced amygdalar volume in individuals with first degree biological relatives diagnosed with an AUD (Dager et al., 2015), a study in which only 3-4% of individuals had a lifetime diagnosis of substance abuse/dependence across groups, which minimized any alcohol-related effects on brain structure. Thus, there now appears to be compelling evidence that smaller amygdalar volume is present in FHP individuals, even in the absence of personal AUDs. However, when characterizing risk based on FHD of AUDs, no significant relationship was shown between degree of risk and amygdalar volume in a group of adolescents with no heavy alcohol use experience (Cservenka et al., 2015). These discrepancies could be due to participant age, experience with alcohol use even in the absence of abuse or dependence, dichotomous measures of familial risk vs. FHD, or type of amygdalar segmentation used. Nevertheless, it is important to consider the alternative explanation that smaller amygdalar volume in adults largely free of alcohol or substance dependence may be a marker of resilience against the development of AUDs. Thus, it will be important for future studies to examine whether these results can be replicated in alcohol-

naïve FHP adolescents, thereby confirming the specific contribution of familial alcoholism to premorbid limbic brain region morphometric alterations.

While hippocampal morphology appears susceptible to the neurotoxic effects of alcohol (De Bellis et al., 2000; Medina et al., 2007; Nagel et al., 2005; Ozsoy et al., 2013), both a study of FHP adults with very low alcohol-related problems (Sjoerds et al., 2013) and a study of FHP adolescents with minimal to no previous substance use (Hanson et al., 2010) indicated significantly different volume of the parahippocampus and hippocampus, respectively, in FHP compared with FHN individuals. The right parahippocampal gyrus showed significantly smaller grey matter density in FHP relative to FHN adults (Sjoerds et al., 2013), while a group-by-gender interaction was present in alcohol-naïve adolescents, such that FHP males had larger left hippocampal volumes relative to FHN males (Hanson et al., 2010). However, the latter study included a small sample of adolescents, so strong conclusions cannot be made. Given a number of studies that have reported memory impairments (Brown et al., 2000) and altered hippocampal volume in AUDs (De Bellis et al., 2000; Medina et al., 2007; Nagel et al., 2005; Ozsoy et al., 2013), future investigations should examine whether familial AUD risk may be contributing to these impairments, and whether there is a sex-specific pattern.

Since several studies have implicated basal ganglia structure and function in AUDs (Beck et al., 2009; Camchong et al., 2013; Makris et al., 2008; Wrase et al., 2007), a few investigations have also begun to examine volume of this region in at-risk individuals. For example, a positive relationship between FHD of alcoholism and nucleus accumbens volume was present in adolescent girls without personal heavy alcohol use (Cservenka et al., 2015), suggesting that larger volume of an incentive processing region may be associated with reward-related behaviors that confer risk for the development of AUDs, as FHD of alcoholism is believed to represent degree of risk. It is possible that mesolimbic circuitry may be atypical in HR individuals, as orbitofrontal cortex (OFC) volume laterality was reported to be reduced in this population – a phenotype that was related to greater impulsivity (Hill et al., 2009), albeit in a sample in which about 20% of individuals had an alcohol or substance abuse/dependence diagnosis. Future studies should also consider assessing the presence of externalizing disorders in adolescents and adults from multiplex families with alcohol dependence, as these diagnoses accounted for volumetric differences in other basal ganglia structures such as the caudate, which was smaller in volume in those at-risk individuals with externalizing disorders relative to those without these diagnoses (Hill et al., 2013a). Thus, future studies need to carefully consider psychiatric comorbidities when examining the contribution of family history risk to brain morphology.

Altered cerebellar morphometry, which has been associated with AUDs, was also found in two studies of HR individuals with some previous history of alcohol and/or substance abuse/dependence (Hill et al., 2007b, 2011). While cerebellar volume was found to be smaller in alcoholics (Sullivan et al., 2000, 2010), two studies found that HR individuals have larger cerebellar volumes relative to LR controls (Hill et al., 2007b, 2011). Altered postural sway reported in familial alcoholism (Hill et al., 2000) could be related to these morphometric findings. It is still uncertain if altered cerebellar volume may be due to delayed synaptic pruning in FHP individuals, or whether this phenotype could potentially be protective for

those with familial alcoholism. Longitudinal investigations of cerebellar volume change are needed in at-risk youth and adults to know if altered cerebellar volume increases risk for or protects against alcoholism.

A study of brain volume and neuropsychological functioning in FHP and FHN early adolescents found that white matter volume as a ratio to intracranial volume (ICV) was significantly related to better performance on reaction time for the Stroop task and correct responses on a Digit symbol task (Silveri et al., 2008). However, this effect was only present in FHN females, suggesting that FH-by-sex interactions may be related to maturation of executive functioning skills, and supports other findings of FH-by-sex effects reported in gray matter volume studies (Cservenka et al., 2015; Hanson et al., 2010).

Further, it should be noted that overall intracranial volume (ICV) may also be affected by familial alcoholism. FHP alcoholics were found to have smaller ICVs than FHN alcoholics or healthy controls (Gilman et al., 2007), suggesting that hereditary or environmental risk factors for AUDs can contribute to overall brain maturation. This finding supports the hypothesis of delayed maturation in alcohol-naïve FHP youth that could put them at risk for maladaptive behaviors. On the other hand, in a different population of adult heavy drinkers and light drinkers, heavy drinkers who had a family history of problem drinking in at least one parent, had smaller cerebrospinal fluid volumes than their FHN peers - effects that were not present in the light drinking group (Cardenas et al., 2005). Thus, it is plausible that the interaction of heavy alcohol use and familial alcoholism as well as the age of onset of use could determine if neurobiological features represent risk for or resilience against AUDs.

Most previous volumetric studies (Table 1) suggest that FHP and HR individuals have altered subcortical brain morphology in reward and affect-related brain regions, including smaller amygdalar volume (Dager et al., 2015; Hill et al., 2001, 2013c), increased NAcc volume in females with higher familial density of the disorder (Cservenka et al., 2015), and display differences in hippocampal volume from their FHN peers (Hanson et al., 2010; Sjoerds et al., 2013). It is possible that decreases in amygdalar volume coupled with increases in NAcc volume could be related to altered emotional processing (Christensen and Bilenberg, 2000; Miranda et al., 2002) and heightened risky drinking (LaBrie et al., 2009) that contributes to vulnerability for developing AUDs in FHP individuals. Furthermore, HR individuals have larger cerebellar volume (Hill et al., 2007b, 2011), a finding opposite to what has been seen in heavy alcohol users (Sullivan et al., 2000, 2010), which could be a risk marker for as opposed to a consequence of alcohol use, or could be indicative of neuroprotective resilience against future cerebellar damage. Further research will need to examine the extent to which cortical areas show alterations in volume in FHP youth or adults as these regions remain understudied.

5. WHITE MATTER MICROSTRUCTURE

White matter integrity, or more restricted diffusion of water along axons, increases over the course of development (Bava et al., 2010; Lebel et al., 2012) and relates to improvements in executive functioning across adolescence (Treit et al., 2014). Thus, decreased white matter integrity could be related to functional deficits in cognition and thereby increase risk for

AUDs. Various studies have reported that relative to FHN adolescents, FHP youth without personal heavy alcohol use have decreased fractional anisotropy (FA) of white matter in pathways that include long-range association tracts, connecting frontal and parietal lobes, such as the superior longitudinal fasciculus (SLF; Acheson et al., 2014c; Herting et al., 2010). Some studies also suggest that degree of risk is negatively related to white matter integrity, such that those with the highest FHD have the lowest FA values (Acheson et al., 2014c). Unfortunately, it is unclear whether this reduced integrity of white matter is a stable characteristic in familial alcoholism or whether lower FA in FHP youth represents developmental delays in white matter maturation. These findings suggest that prevention efforts could focus on strategies to strengthen cognitive functioning prior to the initiation of heavy alcohol use in FHP youth in cognitive domains that are related to reductions in white matter integrity in these adolescents. This is critical, as other studies suggest that interactions between alcohol use and family history of alcoholism may be detrimental to white matter integrity once heavy alcohol use is initiated (Hill et al., 2013b).

Contrary to previous findings, a recent study reported that association, projection, and interhemispheric white matter tracts showed higher FA in alcohol-naïve FHP youth compared with their FHN peers (Squeglia et al., 2014). This could represent compensatory increases in FA in certain pathways, or as the authors hypothesize, could be a marker of more advanced maturation of white matter in FHP adolescents that may increase their susceptibility towards engaging in risky behaviors (Squeglia et al., 2014). Finding associations between white matter integrity and cognitive functioning, as well as assessing risky behaviors, including alcohol use, over the course of adolescence will be needed to answer these questions. Further, many of these studies only included high functioning youth who generally come from affluent families, warranting further research to increase the generalizability of these findings.

Thus, while white matter microstructure has not been extensively explored in studies of familial alcoholism (Table 2), research to date suggests mostly lower FA in FHP relative to FHN youth in white matter tracts connecting fronto-parietal regions, including the SLF, which could explain previous neuropsychological findings of executive functioning deficits in FHP children and adolescents (Corral et al., 2003; Hesselbrock et al., 1991).

6. BRAIN FUNCTIONING

6.1 Inhibitory Control

Multiple studies indicate that inhibitory control brain activity is altered in FHP youth and adults relative to their FHN peers (Acheson et al., 2014a, 2014b; DeVito et al., 2013; Hardee et al., 2014; Heitzeg et al., 2010; Schweinsburg et al., 2004; Silveri et al., 2011), which could explain impulsive characteristics seen in FHP individuals (Nigg et al., 2004; Saunders et al., 2008). Go NoGo tasks, which assess motor impulsivity and engage fronto-striatal circuitry, have been commonly used to study inhibitory control in FHP individuals. While not all studies have reported behavioral differences between FHP individuals and their FHN peers on laboratory Go NoGo tasks, brain response differences have been observed. Reduced brain activity was demonstrated among fronto-parietal regions in 12-14 year old alcohol-naïve FHP adolescents during response inhibition (NoGo vs. Go activity), despite

similar behavioral performance to their FHN peers (Schweinsburg et al., 2004). Additionally, response inhibition may further be derailed in emotionally heated situations, which could exacerbate risk for alcohol abuse, since frontal lobe brain response was reduced during NoGo trials to a greater extent within affective vs. non-affective contexts (Cservenka et al., 2014b). Given alterations in association tracts connecting frontal and parietal areas, such as the SLF, in FHP youth (Herting et al., 2010), functional deficits in these areas could be related to reduced white matter integrity of pathways connecting these regions – tracts that are involved in the maturation of executive functions, such as inhibitory control.

Multiple studies have also found that FHP individuals may exert greater neural effort to perform on par with their FHN peers. Regardless of problem drinking behavior, FHP youth did not deactivate ventral caudate brain response when successfully inhibiting during a Go NoGo task, while FHN youth did deactivate this region (Heitzeg et al., 2010). It is possible that greater neural effort is required in some brain regions for successful performance on this task. In FHP and FHN adults matched on drinking characteristics, family history-by-sex interactions on neural activation during Go NoGo tasks were present. Specifically, in task-positive brain regions such as the anterior insula and inferior frontal gyrus, FHP males had the highest activity during NoGo vs. baseline brain response, which was related to both discounting of rewards and self-reported impulsivity (DeVito et al., 2013). It is possible that increased activity in these brain regions is a function of increased cognitive control effort required for FHP males during successful inhibitions as a result of greater impulsivity in these individuals, or it may be that this neural phenotype provides protection against cognitive control weaknesses.

Furthermore, a longitudinal study of inhibitory control indicated that there are altered trajectories of brain activity during Go NoGo tasks in FHP youth prior to the onset of an AUD. FHP youth showed increased cingulate activity over time, while their FHN peers had reduced fronto-striatal response from baseline to follow-up (Hardee et al., 2014). The authors believed that these findings suggest greater recruitment of inhibitory control regions in FHP youth over time in order to override prepotent responses, which is thought to reflect an altered neurodevelopmental trajectory. Correlating these differing trajectories of brain response during cognitive control to risk-related behaviors that change between childhood and adolescence may help identify patterns of brain activity that predict the onset of heavy alcohol use in FHP youth.

Brain activity differences have also been found between FHP youth and their FHN peers during more complex inhibitory control tasks, such as the counting Stroop or Color-Word Stroop. When contrasting incongruent vs. congruent trials on a counting Stroop task, higher temporo-parietal activity was present in FHP youth (Acheson et al., 2014a). FHD of alcoholism was related both positively and negatively to blood oxygen level-dependent (BOLD) response during a Stroop task in fronto-limbic regions (Silveri et al., 2011).

Overall, these findings indicate both decreased and increased BOLD response during inhibitory control tasks in FHP youth that differs as a function of sex, is related to FHD of alcoholism, changes over the course of development, and is associated with measures of impulsivity (Table 3). Furthermore, in studies of adults with minimal to no alcohol abuse or

dependence, increased BOLD activity during successful inhibition in frontal (DeVito et al., 2013) and parietal regions (Acheson et al., 2014a) could be indicative of a protective neural mechanism against the development of AUDs that is reflective of efficient cognitive control functioning in these individuals.

6.2 Working Memory

Poor working memory skills are associated with AUDs (Ambrose et al., 2001), and deficiencies in working memory functioning could lead to poor decision-making skills, thereby increasing vulnerability for alcohol abuse in FHP individuals (Nagel et al., 2012). Specifically, FHN youth showed significantly more frontal lobe engagement during verbal working memory (VWM) relative to a vigilance control condition than FHP youth who showed comparable activity between those conditions (Cservenka et al., 2012). These findings were also present during spatial working memory (SWM; Mackiewicz Seghete et al., 2013). Thus, while FHN youth showed expected disengagement of frontal regions during vigilance, FHP youth activated these areas, indicating that they still utilize neural resources during a relatively simple attentional and motor response condition, which could explain visuospatial and visuomotor deficits reported in this population (Aronson et al., 1985; Garland et al., 1993; Ozkaragoz et al., 1997; Schaeffer et al., 1984; Tarter et al., 1989). Furthermore, working memory relevant brain areas may not be functioning in synchrony in substance-naïve FHP youth, as these adolescents showed weaker fronto-parietal connectivity during visual working memory than their FHN peers (Wetherill et al., 2012), which complements other reports of lower fronto-parietal activity in FHP adults (Rangaswamy et al., 2004). In both of the aforementioned tasks, visual working memory consisted of maintaining and updating information that occurred in the same spatial location on a computer screen, such as remembering if the color array of dots was the same as the previous screen (Wetherill et al., 2012), or silently counting the total number of target stimuli that occurred infrequently during an experiment, and reporting the total number at the end (Rangaswamy et al., 2004). However, the findings above are opposite to those of Spadoni and colleagues (2013), who reported increased connectivity during SWM between the right superior parietal lobe and left middle frontal gyrus in FHP youth relative to their FHN age-matched peers and an older group of adolescents. During the SWM task, participants had to determine if a nonsense design appeared in the same location on a computer screen as previously presented, and there could be one, two, or three distracters between the two stimuli of the same location. Spadoni and colleagues (2013) describe that differences between their study and previous ones may be due to different neural substrates that are relevant to a visual vs. SWM task, although this remains speculative.

Not only is altered task-positive activity present during working memory tasks in FHP youth, but ineffective disengagement of the default mode network (DMN), brain regions including the medial prefrontal cortex and posterior cingulate gyrus, which display functional synchrony at rest (Greicius et al., 2003), has also been related to degree of familial alcoholism (Table 3). During the resting state, the DMN has been associated with introspective, autobiographical thought processes (Gusnard et al., 2001), but active suppression of DMN areas is critical during task engagement to limit intrusion of task-irrelevant thoughts (McKiernan et al., 2003). The increased suppression of DMN activity

during SWM relative to vigilance was present to a weaker extent in those with higher FHD of alcoholism (Spadoni et al., 2008). Ineffective DMN modulation during working memory, which is critical for adaptive decision-making, may contribute to risky decisions in FHP youth. Since working memory is important for maintaining and updating information, poor modulation of the DMN during working memory, could result in difficulties with making adaptive decisions, which could subsequently increase risky decision-making in FHP adolescents (Nagel et al., 2012).

6.3 Reward Processing and Decision-making

Alterations in mesolimbic circuitry and reward-related response in AUDs, particularly in the nucleus accumbens (NAcc; Beck et al., 2009; Makris et al., 2008; Wrase et al., 2007), has warranted many investigations of reward-related functioning during fMRI tasks in familial alcoholism. As the NAcc is a major site of dopamine release in the mesolimbic pathway (Oades and Halliday, 1987), a preexisting phenotype that increases risk for reward-driven behaviors could be present in familial alcoholism. Despite numerous studies on this question, there is still mixed evidence for premorbid differences in reward-related functioning between FHP and FHN individuals (Table 3). Several studies have implemented the Monetary Incentive Delay (MID) task to examine neural response to reward anticipation and reward feedback. For example, findings by Bjork and colleagues (2008) and Muller and colleagues (2015) suggested that there are no differences in reward anticipation or reward outcome-related response in the NAcc between FHP and FHN youth for monetary or food rewards, respectively. This is in contrast to studies of adults that used the MID task, where less NAcc activation was present during monetary reward anticipation in FHP adults relative to their FHN peers (Andrews et al., 2011). It is possible this blunted response is related to less incentive motivational processing, as FHP young adults showed this pattern whether or not they were anticipating rewards or losses (Yau et al., 2012). However, it is proposed that this phenotype could be a resilience mechanism against future alcohol abuse as this pattern was only present in FHP young adults with no problematic drinking behavior (Yau et al., 2012), while similarly it was present in adults with no past or current alcohol or drug abuse (Andrews et al., 2011).

While the above studies implemented the MID task as their paradigm, another study used a more socially interactive decision-making task, known as the Domino Game task. In this task participants are told they are playing a competitive game against another human opponent, while they play the game against a computer, in which they have to make risky or safe decisions to dispose of all of their domino chips. This study found that risk-taking on the Balloon Analog Risk Task was positively related to reward-associated NAcc activity during the Domino Game task, but not related to family history status (Yarosh et al., 2014). Thus, future studies should attend to whether personality phenotypes or behavior may account better for reward-related brain activity patterns compared with family history status or whether they may potentially mediate the effects of family history status on reward-associated brain response.

Importantly, more research is needed on whether neural activity to rewards is differentially modulated by monetary rewards or primary rewards, such as food or beverages, in FHP

individuals. Research has indicated greater dorsolateral prefrontal cortex and putamen response to monetary reward anticipation in FHP youth compared to their FHN peers, while differences in brain activity to reward receipt were only present during delivery of primary rewards, such as food, and showed that midbrain response was greater in FHP youth than their FHN peers (Stice and Yokum, 2014). However, many of these studies are still confounded by factors that prevent knowing whether family history effects are specific to familial alcoholism or whether lifetime substance use histories of the participants account for some of the findings, as there are frequently subjects with parental histories of multiple substances or an absence of alcohol or substance-naïve participants.

Interestingly, a positron emission tomography (PET) study indicated that tasting beer as opposed to Gatorade induced significantly greater release of dopamine in the striatum in FHP adults than their FHN peers, suggesting inherent differences in striatal dopamine release in response to alcohol in FHP individuals (Oberlin et al., 2013). However, these family history effects were not present when amphetamine was used to stimulate dopamine release in the NAcc (Munro et al., 2006), indicating that inherent risk in FHP individuals may be specific to alcohol-related brain response. Further, the response to alcohol vs. control odors in FHP heavy drinking adults was significantly greater in the medial PFC than in FHN heavy drinking adults – an effect that was absent under intoxication (Kareken et al., 2010). This provides support for the hypothesis that FHP individuals respond differently to rewarding cues than their FHN peers, and that alcohol modulates this response differently in FHP vs. FHN adults. Even visual stimuli themselves, such as the contrast of alcoholic beverages with control images, induced greater BOLD response in visual attention and memory-related brain areas in FHP young adults than their FHN peers, regardless of drinking history (Dager et al., 2013). This could reflect increased sensitivity to rewarding stimuli that may lead to a general predisposition towards risk-related behaviors, including, but not limited to alcohol use.

Moreover, not only is it necessary to understand reward-related brain response in FHP individuals, but it is also critical to know whether risk taking-associated brain activity differs between FHP and FHN youth and adults. Alterations in risky decision-making-related BOLD activity in familial alcoholism would indicate that neural evaluations in the context of risky situations may differ between FHP and FHN individuals, which could explain altered decision-making processes that heighten vulnerability for alcohol abuse in this population. During the Iowa Gambling Task, FHP adults had heightened anterior cingulate cortex (ACC) and caudate activity compared with their FHN peers (Acheson et al., 2009). However, there was no evidence that these differences were related to decision-making components of the task. A study of FHP and FHN youth without a history of personal heavy alcohol or substance use indicated that risky decision-making-related brain response was weaker in FHP youth relative to their FHN peers in key decision-making-related brain regions, such as the DLPFC and cerebellum (Cservenka and Nagel, 2012), which may provide insight into related deficits of planning and problem solving reported on neuropsychological exams in these individuals (Drejer et al., 1985; Schaeffer et al., 1984; Tarter et al., 1989) and help explain maladaptive decisions regarding alcohol use. These findings are relevant as weaker fronto-cerebellar connectivity was also present in FHP youth (Herting et al., 2011), a possible feature or risk that has previously been associated with

AUDs (Sullivan et al., 2003). Thus, it is equally important to focus efforts on clarifying whether decision-making or reward-related neural response (or both) may be atypical in FHP individuals, and if these patterns are present prior to the onset of any heavy alcohol use.

Investigating the connectivity of the NAcc with other brain regions is a new avenue of research that could reveal brain network organization of reward-related brain regions and the integration or segregation of NAcc activity with other neural networks in familial alcoholism. For example, during the MID task, increased coupling of the NAcc with sensorimotor regions involved in habit formation mediated the relationship between sensation seeking and drinking in FHP, but not FHN young adults (Weiland et al., 2013). Thus, perhaps the neural risk profile in FHP individuals is more related to the interaction of the NAcc with other brain regions involved in addiction risk, rather than just the response of the NAcc per se. This interpretation is supported by a study that reported differences in resting state connectivity of the NAcc with other brain regions in FHP vs. FHN adolescents. In FHP youth, the NAcc was less integrated with reward evaluation brain regions, such as the OFC, but also less segregated from brain areas involved in top-down cognitive control processing (Cservenka et al., 2014a). Therefore, altered communication within reward-related networks and between the NAcc and networks involved with top-down cognitive control or motor functioning could be preexisting features of brain organization in FHP youth. Additional studies will be needed to assess structural and functional connectivity between pathways connecting the NAcc with the OFC to investigate the coherence of mesolimbic circuitry in FHP individuals.

6.4 Emotional Processing

Studies in alcoholism report that emotional systems, including limbic brain regions, such as the amygdala show altered responses to affective stimuli in those with AUDs (Marinkovic et al., 2009), and alcoholics also have difficulties with socio-affective communication (Thoma et al., 2013). A premorbid phenotype may exist by which atypical emotional processing could lead to coping related reasons for drinking or deficits in emotional processing could lead to the escalation of socio-emotional problems in FHP individuals. Blunted BOLD response was present to positively valenced emotional faces in brain regions associated with socio-emotional processing, such as the temporal lobe, in largely alcohol-naïve FHP youth compared with their FHN peers (Cservenka et al., 2014b). Similarly, HR adolescents/young adults (some of whom met criteria for alcohol dependence or other psychiatric disorders) displayed blunted right middle temporal gyrus activity during a theory of mind task requiring emotional judgments based on pictures of eyes (Hill et al., 2007a). These findings suggest that socio-emotional systems and processing of affective information may be altered in familial alcoholism, and since similar responses have been seen across a variety of emotional facial stimuli, social cues themselves may be processed differently in this population.

Amygdalar activity may also be associated with disinhibited temperament, as response to fearful stimuli in this region is thought to reflect a “breaking” mechanism, by which risk-taking may be curtailed (Ernst et al., 2006). Hyporesponsive amygdalar activity to fearful faces in FHP young adults, which was correlated with impulsive temperament, indicates that

reduced limbic response to negatively valenced stimuli could drive engagement with risky behaviors (Glahn et al., 2007). However, blunted amygdalar response to negatively valenced emotional faces was not present in largely alcohol-naïve FHP youth (Cservenka et al., 2014b), which could be due to differences in tasks used, age of participants, or analytical strategies. However, this also begs the question of alcohol-induced alterations that could be driving findings in adult studies, as blunted amygdalar response to emotional words was present in vulnerable (problem drinkers), but not resilient children of alcoholics (Heitzeg et al., 2008).

Importantly, some of the differences in emotional processing between FHP and FHN adolescents (Table 3) are subtle. During a task with presentation of subliminal emotional faces, FHN youth deactivated regions associated with attentional control, such as the superior parietal lobe, in the presence of both fearful and neutral subliminal faces (Peraza et al., 2015). However, FHP youth only deactivated this region during the presentation of fearful subliminal faces. While neutral faces are considered salient during adolescence (Thomas et al., 2001), they may be less salient for FHP youth, which thereby leads them to not deactivate attention-related brain regions in their presence (Peraza et al., 2015).

More studies are necessary to examine the extent to which emotional processing and regulation deficits may be atypical in fMRI studies of FHP individuals. These studies may discover unique neural characteristics of risk towards AUDs in familial alcoholism that are related to stress, coping, and affect regulation, which would not be captured by solely examining brain activity during top-down executive functioning processing tasks.

6.5 Magnetic Resonance Spectroscopy

Only a few studies to date have examined whether brain metabolites differ by family history status (Table 3), with one of these being in a sample of adolescents and young adults with minimal and light alcohol use, respectively (Cohen-Gilbert et al., 2015). Glutamine/glutamate (Gln/Glu) amino acid ratio is believed to represent metabolic turnover that can be used as a marker for neurotransmission (Ongur et al., 2011), and has been shown to be altered as a function of alcohol use (Meyerhoff, 2014). Unexpectedly, Gln/Glu ratios in the anterior cingulate cortex (ACC) were higher in FHN young adults relative to adolescents, but this pattern was not observed in the FHP groups (Cohen-Gilbert et al., 2015). The authors described that these differences were largely due to FHP adolescents already resembling young adults in Gln/Glu ratio. Interestingly, motor impulsivity was negatively related to Gln/Glu ratio in the ACC among FHP adolescents, which was believed to reflect a neuroprotective mechanism (Cohen-Gilbert et al., 2015). Another spectroscopy study, albeit in FHP and FHN adults with alcohol abuse and dependence, found that N-acetylaspertate (NAA), used to infer axonal or neural damage, was not lost to a greater extent in FHP heavy drinkers compared with FHN heavy drinkers, suggesting another potential mechanism of resilience conferred by familial alcoholism, even in adults who have years of alcohol misuse (Meyerhoff et al., 2004). Given the sparsity of research in this area, significantly more work is needed to understand the neurochemical profile related to familial alcoholism.

7. CONCLUSIONS

While there is no conclusive evidence for which neural markers of risk in FHP and HR individuals are most related to the higher rates of AUDs seen in this population, many findings have been replicated (Figure 1). Smaller amygdalar volume (Dager et al., 2015; Hill et al., 2001, 2013c) and larger cerebellar volume (Hill et al., 2007b, 2011) have been found in FHP and HR individuals relative to their FHN peers. Future studies that correlate neuropsychological, behavioral, and/or personality variables to these volumetric findings are needed to better understand the functional consequences of altered brain morphometry in familial alcoholism.

Long-range association tracts, such as the SLF, have shown reduced white matter integrity in FHP and HR youth and young adults (Acheson et al., 2014c; Herting et al., 2010; Hill et al., 2013b), while fronto-parietal brain activity has been reduced in largely alcohol-naïve adolescents during inhibitory control in both affective (Cservenka et al., 2014b) and non-affective (Schweinsburg et al., 2004) Go NoGo tasks. FHP adolescents showed comparable activity during both verbal (Cservenka et al., 2012) and spatial working memory (Mackiewicz Seghete et al., 2013) and vigilance in the frontal lobe, while FHN youth showed differences in brain activity between those conditions. Fronto-parietal connectivity (Wetherill et al., 2012) and brain activity (Rangaswamy et al., 2004) was also reduced in FHP individuals during working memory and a visual oddball task compared with their FHN peers. Together, these functional and structural findings suggest executive functioning systems may be compromised in those with familial risk for alcoholism.

It is uncertain whether reward processing is altered in FHP individuals. Previous studies reported both null effects (Bjork et al., 2008; Muller et al., 2015) and reduced NAcc brain activity during reward anticipation and/or reward receipt (Andrews et al., 2011; Yau et al., 2012), but most research has utilized paradigms with monetary rewards. Studies that use alcohol as a reward either by administering its taste (Oberlin et al., 2013), or odor (Kareken et al., 2010), or presenting alcohol-related cues (Dager et al., 2013), have all indicated increased brain response to alcohol, and this was present across many brain areas, including frontal, reward-related, visual attention, and memory-associated regions. Finally, in response to emotional stimuli, temporal lobe response was reduced in FHP and HR individuals compared with their FHN peers (Cservenka et al., 2014b; Hill et al., 2007a), which is indicative of alterations in socio-affective processing.

Future studies will need to better understand brain network organization in FHP individuals. Is connectivity of brain regions atypical in this population, and which structural and/or functional neural markers are predictive of the development of AUDs? Longitudinal study designs will be critical for answering these questions. Continued efforts towards identifying neural markers that are most predictive of AUD risk will allow for the implementation of neurobiologically informed prevention efforts to reduce the prevalence of AUDs in FHP individuals. Specifically, information gleaned from the studies discussed in this review and future neuroimaging studies of familial alcoholism could be helpful in identifying neural structures, connections, or functions that could be strengthened, modified, or altered with neurobehavioral methods to promote healthy brain functioning and reduce the incidence of

AUDs. Similar strategies have recently been examined in neuroimaging studies on the mechanisms of behavior change, which utilize information on brain activity to predict the success of psychosocial interventions (Feldstein Ewing et al., 2011). Developing tasks that promote strong executive functioning skills, such as increased inhibitory control, may be one of many methods that could minimize potential risks associated with reductions in white matter integrity of fronto-parietal pathways (Acheson et al., 2014c; Herting et al., 2010) and altered prefrontal functioning (Cservenka et al., 2012; Cservenka and Nagel, 2012; Schweinsburg et al., 2004) that may be related to elevated risk for AUDs in familial alcoholism.

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Highlights

- Family history of alcoholism (FHP) is associated with premorbid subcortical and cerebellar brain volumetric alterations.
- FHP individuals have both increased and decreased white matter microstructure integrity relative to their peers (FHN).
- Brain activity differences are present between FHP and FHN individuals during executive functioning, reward, and emotion processing tasks.
- Understanding premorbid neural characteristics in familial alcoholism may help inform studies focused on reducing the incidence of alcohol abuse in at-risk youth and adults.

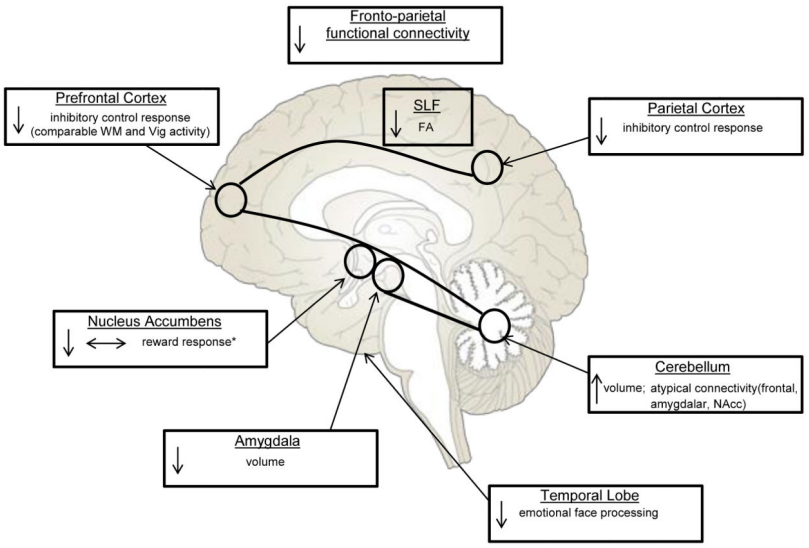

Figure 1. Replicated Findings in Youth and Adults with a Family History of Alcoholism

This figure illustrates volumetric, white matter microstructure, and functional brain imaging findings that have been replicated in neuroimaging studies of family history of alcoholism. FA = fractional anisotropy, SLF = superior longitudinal fasciculus, Vig = vigilance, WM = working memory, *for monetary rewards, ↓ smaller/decreased, ↑ larger/increased, ↔ no change

Table 1

Brain Volume Findings in Familial Alcoholism

Structure	Study	Age in Years (M±SD)	Population (N)	Alcohol Use[1]	Main Findings[2]
Amygdala	Hill et al., 2001	HR=17.6±2.9, LR=17.3±2.2	17 HR, 17 LR	18.2% A/D dependence in HR	↓R Amyg in HR
	Hill et al., 2013c	HR=18.2±4.2, LR=17.7±5.8	71 HR, 58 LR	N=10 with A/D dependence	↓Amyg in HR
	Cservenka et al., 2015	M=14.1±1.3, F=14.6±1.3	75 M/65 F, FHM/FHP	No heavy A/D use[4]	↔FHD on Amyg
	Dager et al., 2015	1st ± with AUD=52.6±13, Controls=40.2±16[3]	137 1st ° with AUD 227 Controls	3-4% lifetime substance abuse/dependence	↓Amyg in subjects with 1st ° relative with AUD
Hippocampus	Hanson et al., 2010	FHP=13.5±0.9, FHN=13.6±0.9	15 FHP, 15 FHN	Minimal/no previous substance use	↑L Hipp in FHP M vs. FHN M
	Sjoerds et al., 2013	FHP=38.2±9.8, FHN=38.1±10.7	36 FHP, 107 FHN	AUDIT(mean): FHP=3.3, FHN=3.9	↓R PHG in FHP
Nucleus Accumbens	Cservenka et al., 2015	M=14.1±1.3, F=14.6±1.3	75 M/65 F, FHM/FHP	No heavy A/D use[4]	↑FHD, larger NAcc
Orbitofrontal Cortex	Hill et al., 2009	HR=18.3±4.5, LR=16.7±4.9	63 HR, 44 LR	N=22 A/D abuse/dependence	↓R/L OFC ratio in HR
Caudate	Hill et al., 2013a	HR=18.1±4.2, LR=17.6±5.8	71 HR, 59 LR	N=23 A/D abuse/dependence	↔risk on caudate[5]
Cerebellum	Hill et al., 2007b	HR=17.6±2.9, LR=17.5±2.2	17 HR, 16 LR	N=5 A/D dependence in HR	↑cerebellum in HR
	Hill et al., 2011	HR=18.3±4.2, LR=17.8±5.8	71 HR, 60 LR	N=24 A/D abuse/dependence	↑cerebellum in HR[6]
Intracranial Volume	Gilman et al., 2007	LO=43.9±8.5, EO=37.0±8.7, Controls=34.6±10.1	LO (64 FHP, 38 FHN), EO (82 FHP, 47 FHN), 114 Controls	N=231 alcoholics (with and without family history of alcoholism)	↓ICV in FHP alcoholics
White Matter	Silveri et al., 2008	FHP M=12.6±2.7, FHP F=12.4±3.0, FHN M=12.6±2.5, FHP F=12.4±2.1	17 FHP, 16 FHN	<3 lifetime episodes of A/D use for all participants	Information processing speed related to WM/ICV in FHN F
Cerebrospinal Fluid	Cardenas et al., 2005	HD M=40.9±9.7, HD F=43.6±10.4 (ages not specified based on family history)	26 FHP HD, 22 FHN HD	Heavy drinkers >100 or >80 drinks/month for M, F, respectively for three years[7]	↓frontal, parietal, and occipital CSF in FHP HD

Amyg = amygdala; A/D = alcohol/drug; AUD = alcohol use disorder; AUDIT = alcohol use disorders identification test; CSF = cerebrospinal fluid; EO = early onset alcoholic; F = female; Hipp = hippocampus; HR = high risk (offspring from multiplex families with alcohol dependence in which two adult brothers with alcohol dependence identified); FHD = family history density (the degree of familial alcoholism in one's family); FHM = family history mild (individual with at least one 2nd degree relative with AUD); FHN = family history negative (individual with no 1st (or in some cases no 1st or 2nd) degree relatives with AUD); FHP = family history positive (individual with at least one 1st degree relative with AUD or in some cases at least two or more 2nd degree relatives with AUD); HD = heavy drinkers (>100 drinks/month for males and >80 drinks/month for females for three years); ICV = intracranial volume; L = left; LO = late onset alcoholic; LR = low risk (offspring from families in which no Axis I alcohol dependence identified); M = male; NAcc = nucleus accumbens; OFC = orbitofrontal cortex; PHG = parahippocampal gyrus; R = right; WM = white matter;↓ = smaller or decreased; ↑ = larger or increased; ↔ = no difference/no effect;

[1] only alcohol use characteristics are noted, even though some studies also included participants with lifetime diagnoses of other psychiatric disorders not listed in this table (i.e. depression, anxiety, externalizing disorders). In some studies results are reanalyzed without subjects who met criteria for A/D dependence, of which details are not included here.

[2] relative to the LR, control, or FHN group, unless otherwise specified.

[3] study sample also included individuals with lifetime, current, or past AUD diagnoses, and unaffected individuals with 2nd-5th degree relatives with AUDs for which participant characteristics are not listed in table.

[4] no more than 10 lifetime drinks and 2 drinks/occasion, no more than 5 uses of marijuana, 4 cigarettes/day, or any other substance use.

[5] but ↓caudate in those with externalizing disorders in sample.

[6] when 24 subjects with substance use disorder removed from sample (N=107).

[7] light drinkers included in study not described in Table.

Table 2

White Matter Microstructure Findings in Familial Alcoholism

Study	Age in Years (M±SD)	Population (N)	Alcohol Use[1]	Main Findings[2]
Herting et al., 2010	FHP=13.8±1.5, FHN=13.8±1.6	15 FHP, 19 FHN	No heavy A/D use[3]	↓FA in prefrontal, subcortical, temporal tracts in FHP
Hill et al., 2013b	HR M=25.3±5.0, LR M=21.5±5.2 HR F=24.7±5.1, LR F=24.0±5.7	44 HR, 37 LR	N=32 A/D abuse/dependence	Risk x exposure interactions in ILF, SLF, FM, ↓FA in HR
Acheson et al., 2014c	FHP Y=12.9±1.2, FHN Y=12.9±1.1 FHP A=24.1±4.2, FHN A=24.5±2.7	80 FHP Y, 34 FHN Y, 25 FHP A, 30 FHN A	No regular substance use in Y[4] N=4 past alcohol abuse in A	↓FA in FOF, SCNin FHP Y; ↓FA with ↑FHD in ACN, genu of CC in FHP A
Squeglia et al., 2014	FHP=13.7±0.7, FHN=13.5±0.6	48 FHP, 46 FHN	0-2 days of lifetime alcohol use	↑FA in 19 regions in FHP

A = adult; ACN = anterior corona radiata; A/D = alcohol/drug; CC = corpus callosum; F = female; FA = fractional anisotropy; HR = high risk (offspring from multiplex families with alcohol dependence in which two adult brothers with alcohol dependence identified); FHD = family history density (the degree of familial alcoholism in one's family); FHN = family history negative (individual with no 1st (or in some cases no 1st or 2nd) degree relatives with AUD); FHP = family history positive (individual with at least one 1st degree relative with AUD or in some cases at least two or more 2nd degree relatives with AUD); FM = forceps major; FOF = fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; LR = low risk (offspring from families in which no Axis I alcohol dependence identified); M = male; SCN = superior corona radiata; SLF = superior longitudinal fasciculus; Y=youth; ↓ = smaller or decreased; ↑ = larger or increased; ↔ = no difference/no effect;

[1] only alcohol use characteristics are noted, even though some studies also included participants with lifetime diagnoses of other psychiatric disorders not listed in this table (i.e. depression, anxiety, externalizing disorders). In some studies results are reanalyzed without subjects who met criteria for A/D dependence, of which details are not included here.

[2] relative to the LR, control, or FHN group, unless otherwise specified.

[3] no more than 10 lifetime drinks and 2 drinks/occasion, no more than 5 uses of marijuana, 4 cigarettes/day, or any other substance use.

[4] no more than once/month substance use for six consecutive months.

Table 3

Brain Function Findings in Familial Alcoholism

	Study	Age in Years (M±SD)	Population (N)	Alcohol Use[1]	Main Findings[2]
Inhibitory Control	Schweinsburg et al., 2004	FHP=13.8±1.5, FHN=13.8±1.6	12 FHP, 14 FHN	None	↓BOLD in MFG/parietal cortex in FHP for nogo vs. go
	Heitzeg et al., 2010	FHP=19.0±1.6, FHP+P=19.3±1.3 FHN=19.2±1.9	20 FHP, 21 FHP+P, 20 FHN	N=8 A/D dependence in FHP+P	↓BOLD in ventral caudate in FHN; not present in FHP groups for nogo vs. go
	Silveri et al., 2011	FHP=13.2±3.2, FHN=13.8±2.6	18 FHP, 14 FHN	No current or >3 lifetime episodes of A/D use	↑FHD, ↑BOLD in frontal/insular regions in interference-color naming
	DeVito et al., 2013	FHP=29.8±11.5, FHN=33.3±13.5	28 FHP, 31 FHN	No A/D abuse/dependence	↑BOLD in frontal/insular regions in FHP during successful inhibition
	Hardee et al., 2014	Age Range: FHP=7.85-16.74, FHN=7.58-16.83	43 FHP, 30 FHN	N=5 A/D use at baseline; N=13 A/D use at follow-up	↓BOLD in caudate and MFG in FHN over time; absent in FHP
	Acheson et al., 2014a	FHP=23.6±4.0, FHN=24.0±2.6	24 FHP, 28 FHN	N=3 past alcohol/abuse	↑BOLD in parietal, temporal regions in FHP for incongruent vs. congruent
	Acheson et al., 2014b	FHP=12.9±1.0, FHN=12.9±1.1	72 FHP, 32 FHN	3-7% of youth ever used A/D	↑BOLD in cingulate, temporal, frontal regions in FHP in Go/NoGo blocks
	Cservenka et al., 2014b	FHP=14.9±1.3, FHN=14.7±1.1	19 FHP, 17 FHN	No heavy A/D use[3]	↓BOLD in fronto-striatal-parietal regions in FHP during nogo in emotional vs. non-emotional contexts
Working Memory	Spadoni et al., 2008	13.3±0.8	72 FHP and FHN	Minimal lifetime use of A/D	↑FHD, ↓BOLD in vigilance vs. SWM in cingulate, MeFG
	Cservenka et al., 2012	FHP=14.0±0.9, FHN=14.2±0.7	19 FHP, 16 FHN	No heavy A/D use[3]	FHP no difference between VWM and vig BOLD in frontal regions
	Mackiewicz Seghete et al., 2013	FHP=14.5±0.9, FHN=14.2±0.7	18 FHP, 16 FHN	No heavy A/D use[3]	FHP no difference between SWM and vig BOLD in frontal regions
Reward Processing/ Risky Decision-making	Bjork et al., 2008	COA=13.9±0.4, Controls=13.8±0.4	13 COA, 13 Controls	Not discussed	No differences in reward anticipation or receipt
	Acheson et al., 2009	FHP=24.0±0.8, FHN=23.0±0.7	15 FHP, 19 FHN	No A/D abuse/dependence	↑BOLD in ACC, caudate in FHP during IGT
	Andrews et al., 2011	FHP=33.7±13.6, FHN=33.6±14.4	19 FHP, 30 FHN	No past/current A/D abuse	↓BOLD in NAcc, insula, OFC in FHP during reward anticipation

	Study	Age in Years (M±SD)	Population (N)	Alcohol Use[1]	Main Findings[2]
	Cservenka et al., 2012	FHP=14.2±0.7, FHN=14.2±0.8	18 FHP, 13 FHN	No heavy A/D use[3]	↓BOLD in frontal lobe and cerebellum in FHP during risky vs. safe decision-making
	Yau et al., 2012	COA=20.2±1.2, Controls=20.1±1.3	20 COAs, 20 Controls	A/D use present	↓BOLD in NAcc in COA during reward anticipation, lower in low-risk COA vs. high-risk COA
	Stice and Yokum, 2014	FHP=14.7±0.9, FHN=14.9±1.0	N=26 FHP, N=26 FHN for any substance	No >1/week use of psychoactive substances	↑BOLD in midbrain in FHP during food reward receipt; in DLPFC, putamen for anticipated monetary receipt
	Yarosh et al., 2014	FHP=26.2±5.6, FHN=25.5±6.3	40 FHP, 29 FHN	No current/past A/D abuse/dependence	↑impulsivity, ↑BOLD for reward-punishment across both FHP and FHN
	Muller et al., 2015	FHP=14.7±0.4, FHN=14.7±0.3	77 FHP, 77 FHN	Some lifetime A/D use	No differences between FHP and FHN for NAcc reward anticipation/receipt
Alcohol/Drug Stimuli	Munro et al., 2006	FHP=21.7±2.8, FHN=21.9±3.1	11 FHP, 30 FHN	<30 alcoholic drinks/month	No differences in BP or DA release between FHP and FHN
	Kareken et al., 2010	FHP=23.9±2.3, FHN=23.4±2.9	14 FHP heavy drinkers, 12 FHN heavy drinkers	AUDIT(mean): FHP=10.4, FHN=12.3	↑BOLD in MeFG for alcohol vs. appetitive odors in FHP, dampened by acute alcohol
	Dager et al., 2013	FHP=19.3±0.8, FHN=19.2±0.7 heavy drinkers; FHP=18.9±1.0, FHN=19.4±0.6 light drinkers	10 FHP heavy drinkers, 25 FHN heavy drinkers, 11 FHP light drinkers, 19 FHN light drinkers	24-92% A/D abuse/dependence present in heavy drinkers	↑BOLD in temporo-parietal, hippocampal areas in FHP for repeated alcohol images
	Oberlin et al., 2013	FHP=24.6±3.8, FHA=24.7±3.9, FHN=24.8±3.2	12 FHP, 18 FHA, 19 FHN	N=4 alcohol dependence	Beer flavor stimulates DA release in FHP
Emotional Processing	Glahn et al., 2007	FHP=23.0±1.1, FHN=24.0±1.2	9 FHP, 8 FHN	AUDIT(mean): FHP=3.6, FHN=3.5	↓BOLD in Amyg in FHP during face vs. shape matching
	Hill et al., 2007a	HR=22.6±3.3, LR=23.6±4.2	8 HR, 8 LR	N=3 A/D dependence	↓BOLD in MTG, SFG, IFG, in FHP during emotion vs. gender eyes task
	Heitzeg et al., 2008	FHP Resilient=18.4±1.0, FHP Vulnerable=17.5±1.3, FHN Controls=17.2±1.6	11 FHP Vulnerable, 11 FHP Resilient, 6 FHN Controls	27.3% A/D dependence in Vulnerable group	↑BOLD in OFC in resilient vs. controls during negative vs. neutral words
	Cservenka et al., 2014b	FHP=14.9±1.3, FHN=14.7±1.1	19 FHP, 17 FHN	No heavy A/D use[3]	↓BOLD in STG in FHP to happy vs. calm faces
	Peraza et al., 2015	FHP=13.7±1.5, FHN=13.7±1.6	14 FHP, 15 FHN	No heavy A/D use[3,4]	↓BOLD in SPL in FHP to fearful vs. neutral subliminal faces
Connectivity	Herting et al., 2011	FHP=13.5±1.3, FHN=13.6±1.6	13 FHP, 14 FHN	Alcohol and substance-naïve	↓fronto-cerebellar connectivity in FHP
	Wetherill et al., 2012	FHP=13.6±0.6, FHN=13.5±0.7	20 FHP, 20 FHN	Substance-naïve	↓fronto-parietal connectivity in FHP

	Study	Age in Years (M±SD)	Population (N)	Alcohol Use[1]	Main Findings[2]
	Spadoni et al., 2013	FHP=13.3±0.9, FHN=13.2±0.8, OA=17.7±1.1	24 FHP, 26 FHN, 35 OA	Minimal exposure to alcohol, cigarettes, and marijuana	Removal of SPL-MFG pathway reduced model fit more for FHP than FHN; connectivity of OA more like FHN
	Weiland et al., 2013	FHP=20.1±1.3, FHN=20.1±1.3	49 FHP, 21 FHN	N=8 A/D abuse or dependence	↑connectivity NAcc-SMA and NAcc-postcentral gyrus connectivity during reward anticipation in FHP
	Cservenka et al., 2014a	FHP=14.6±1.3, FHN=14.3±1.3	47 FHP, 50 FHN	No heavy A/D use[3]	↓NAcc-IFG segregation and NAcc-OFC integration in FHP
Magnetic Resonance Spectroscopy	Meyerhoff et al., 2004	HD=41.3±9.4 (age not specified based on family history)	28 FHP HD, 18 FHN HD	Heavy drinkers >100 or >80 drinks/month for M, F, respectively for three years[5]	↑NAA in frontal white matter, ↓mI in brainstem in FHP HD
	Cohen-Gilbert et al., 2015	FHP=13.7±1.0, FHN=13.6±0.8 adolescents; FHP=21.0±1.9, FHN=21.7±1.6 young adults	12 FHP, 19 FHN adolescents, 7 FHP, 22 FHN young adults	<3 lifetimes uses of alcohol for adolescents; ≤3 drinks/occasion or 5 occasions in 30 days for young adults	↑Gln/Glu ratio in FHN young adults vs. adolescents in ACC

ACC = anterior cingulate cortex; Amyg = amygdala; A/D = alcohol/drug; AUDIT = alcohol use disorders identification test; BOLD = blood oxygen level-dependent; BP = binding potential; COA = children of alcoholics; DA = dopamine; DLPFC = dorsolateral prefrontal cortex; FHA = family history ambiguous; FHD = family history density (the degree of familial alcoholism in one's family); FHM = family history mild (individual with at least one 2nd degree relative with AUD); FHN = family history negative (individual with no 1st (or in some cases no 1st or 2nd) degree relatives with AUD); FHP = family history positive (individual with at least one 1st degree relative with AUD or in some cases at least two or more 2nd degree relatives with AUD); FHP+P = family history positive problem drinker; Gln/Glu = glutamine/glutamate ratio; HR = high risk (offspring from multiplex families with alcohol dependence in which two adult brothers with alcohol dependence identified); IFG = inferior frontal gyrus; IGT = Iowa Gambling Task; LR = low risk (offspring from families in which no Axis I alcohol dependence identified); MFG = middle frontal gyrus; MeFG = medial frontal gyrus; mI = myoinositol; MTG = middle temporal gyrus; NAA = N-acetylaspertate; NAcc = nucleus accumbens; OA = older adolescents; OFC = orbitofrontal cortex; SFG = superior frontal gyrus; SMA = supplementary motor area; SPL = superior parietal lobule; STG = superior temporal gyrus;SWM = spatial working memory; VWM = verbal working memory; ↓ = smaller or decreased; ↑ = larger or increased; ↔ = no difference/no effect

[1] only alcohol use characteristics are noted, even though some studies also included participants with lifetime diagnoses of other psychiatric disorders not listed in this table (i.e. depression, anxiety, externalizing disorders). In some studies results are reanalyzed without subjects who met criteria for A/D dependence, of which details are not included here.

[2] relative to the LR, control, or FHN group, unless otherwise specified.

[3] no more than 10 lifetime drinks and 2 drinks/occasion, no more than 5 uses of marijuana, 4 cigarettes/day, or any other substance use.

[4] one youth had 3 drinks of alcohol on one occasion.

[5] light drinkers included in study not described in Table.