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Review

# 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.


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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 multigenerational 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