

# Neurophysiological Correlates and Differential Drug Response in Subjects With a Family History of an Alcohol Use Disorder

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## Abstract

A family history of an alcohol use disorder (AUD) has been shown to increase one's risk of developing an AUD. Additionally, a positive family history of AUD (family history positive (FHP)) has neurobiological and neuropsychopharmacological consequences, and this review summarizes differential drug response as well as neuroanatomical and neurocognitive correlates. FHP status is related to altered responses to a number of drugs, including substances with abuse liability like alcohol, opioids, amphetamines, and ketamine. FHP individuals demonstrate fewer aversive effects and more rewarding response to both alcohol and subanesthetic dose ketamine. Ketamine is a rapid-acting antidepressant, and several studies have reported that ketamine is more effective for FHP treatment-resistant depressed individuals. In short, the reviewed neurophysiological differences may contribute to ketamine's enhanced antidepressant efficacy in FHP patients. Volumetric differences in the amygdala, nucleus accumbens, neocortex, and cerebellum are commonly reported. Furthermore, FHP has also been associated with altered neurocognitive performance, e.g., increased impulsivity. The imaging and psychological literature supports a neurodevelopmental lag hypothesis in FHP youth. The review will further discuss these findings in depth.

## Keywords

family history of alcohol dependence, familial alcoholism, ketamine, neuroimaging, treatment-resistant depression

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## Introduction

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition defines alcohol use disorder (AUD) as the presence of at least 2 of 11 possible symptoms including alcohol tolerance, withdrawal symptoms, alcohol craving, unsuccessful attempts to stop or reduce drinking, and frequently drinking more than intended.<sup>1</sup> AUDs are highly prevalent disorders, with a 12-month prevalence rate of 12.7% among adults in the United States,<sup>2</sup> with men being more likely to have an AUD than women.<sup>1,2</sup> Of the global population, the estimated 12-month prevalence rate of AUD is 3.6% (of people aged 15–64), indicating AUDs are more common in the United States than other countries.<sup>1</sup> AUDs are associated with negative outcomes such as work absences, low work productivity, homelessness, suicide, work and vehicular accidents, and violence. Worldwide, it is estimated that 3.8% of all deaths are alcohol-related.<sup>1</sup> Additionally, chronic alcohol use is related to a number of neurocognitive impairments<sup>3</sup> and changes in brain structure and

connectivity.<sup>4</sup> Several factors lead to the development of AUDs, with one of the most influential factors being genetics.

AUDs are highly heritable.<sup>5–8</sup> Heritability estimates range from 30% to 60%<sup>1,6,8,9</sup> with shared environment with someone affected with an AUD explaining an additional 10% of risk.<sup>8</sup> Having a family history of an AUD (family history positive (FHP)) is also linked to differences in brain structure, cognitive functioning, and social outcomes.<sup>10</sup> FHP is frequently studied as an at-risk biomarker, with newer research examining the genetic and neurobiological mechanisms by which heritable

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risk for AUD is transmitted, as well as FHP in relation to response to substances.<sup>10,11</sup>

Operational definitions of FHP status vary from study to study. Early researchers identified FHP individuals as sons of alcoholic fathers.<sup>12,13</sup> Many studies have looked at family history density, i.e., quantity and/or relatedness of affected family members, and categorized subjects as either high risk (HR) or low risk (LR) for AUD, rather than dichotomizing presence or absence of family history.<sup>14,15</sup> With that said, researchers have typically defined FHP as having at least one first-degree relative with an AUD and/or at least one or two second-degree relatives with an AUD. As corollary, family history negative (FHN) individuals have been defined as all first (and sometimes also second)-degree relatives are without an AUD.<sup>16,17</sup> Methods for determining family history have varied as well. For example, many studies use family history questionnaires delivered to the participant, others ask informants knowledgeable of participant family history (often relatives), and others have identified individuals who meet AUD criteria and then studied their relatives/offspring.<sup>17</sup>

Variety in operational definitions aside, several differences regarding FHP individuals are identified in the literature. This review summarizes these findings. After a brief discussion of stress and psychosocial impairment, we review drug response in FHP subjects with a particular emphasis on responsiveness to alcohol and ketamine. We then review neuroanatomical and neurocognitive correlates of FHP.

### *Increased Stress and Psychosocial Impairment Associated With FHP*

FHP is linked to a number of stressful life experiences. In a qualitative study of adult FHP experiences with their alcoholic parents, participants described violence and increased abuse towards spouses, siblings, and self when their AUD parent was intoxicated as well as *parentification*, where the child is placed into the caregiver role for their parent(s) and/or siblings.<sup>18</sup> FHP subjects described poor relationships with the alcoholic parent and other family members.<sup>18</sup> FHP youth demonstrate increased externalizing and internalizing problems, poorer academic performance, increased mental disorders, and lower social competence.<sup>19</sup> Externalizing behaviors and poorer self-regulation have been reported as young as one year old.<sup>19</sup> These negative outcomes continue to manifest into adulthood. FHP adults report continued difficulties with decreased self-esteem,<sup>18,19</sup> relationships,<sup>18</sup> interpersonal anxiety,<sup>19</sup> adjustment skills,<sup>18</sup> and poor academic performance.<sup>19</sup>

Another notable psychosocial impairment associated with FHP is increased rates of substance use disorders (SUD). In probands with AUD, 8.3% of first-degree

relatives had a drug use disorder (not including AUD or nicotine use disorder) and 35.5% had AUD. In control probands, only 3.5% of relatives had a drug use disorder and 14.9% had AUD.<sup>7</sup> FHP adults also drink more alcohol in response to stress compared to their FHN counterparts.<sup>20</sup> This increase rate of alcohol consumption may be due to differential responsiveness, which will now be discussed.

### *FHP and Differential Drug Response*

**Alcohol.** It comes as no surprise that FHP individuals respond differently to alcohol and alcohol-related cues. FHP subjects appear to be immediately more sensitive to alcohol consumption but quickly develop acute tolerance to its intoxicating effects.<sup>21</sup> Specifically, Morzorati et al.<sup>21</sup> utilized the alcohol clamp method, which entails administering intravenous (IV) alcohol to subjects until desired blood alcohol content (BAC) is reached. Once target BAC is achieved, researchers continually acquire breathalyzer readings and adjust the alcohol infusion rates accordingly to maintain (or “clamp”) desired BAC. FHP participants reported feeling more intoxicated during the ramp phase compared to FHN participants. However, as the clamp was maintained, FHP participants seemed to become more tolerant, i.e., reported feeling less “ascending limb” intoxication effects like euphoria and disinhibition, compared to FHN participants.<sup>21</sup> This acute tolerance may be another mechanism by which the risk of alcoholism leads to increased consumption, as FHP subjects required progressively greater amounts of alcohol to maintain rewarding intoxicating effects.

As alluded to above, there is an accepted biphasic model of alcohol response: the “ascending limb,” which occurs as BAC rises, and descending limb, which occurs as BAC falls. Subjective stimulant effects of alcohol are more common in the ascending limb, while subjective sedative effects are more common in the descending limb.<sup>22</sup> FHP individuals endorse more stimulant effects in response to alcohol.<sup>23,24</sup> When examined in light versus heavy drinkers, heavy drinkers reported stimulant effects shortly after consuming alcohol and, as the BAC fell, experienced less sedative effects than other groups.<sup>25</sup>

Schuckit and coworkers<sup>26–28</sup> have coined the term “low level of response” (LLR) primarily to describe FHP individuals having attenuated responsivity to alcohol challenge (and greater risk of progression to AUD). For example, those subjects that demonstrated LLR as measured by subjective reports of intoxication, body sway, hormone levels, and electrophysiological/myological testing were more likely to be FHP and subsequently develop AUDs.<sup>27,28</sup> In sum, with the notable exception of the Morzorati et al.<sup>21</sup> study finding that FHP individuals have a higher level of response in the

initial phase of the alcohol clamp, these studies provide compelling evidence linking family history of AUD, LLR, and alcohol dependence.

Further, alcohol expectancies have been shown to correlate with their reported effects. In one study, FHN participants were generally more sensitive to alcohol than FHP counterparts; however, expectancies of alcohol predicted FHP participants' reports of intoxication, while BAC predicted self-reported intoxication of the FHN participants.<sup>29</sup> Furthermore, FHP young adults had fewer negative associations with alcohol than their FHN counterparts; however, the two groups did not differ on perceived positive consequences of alcohol use.<sup>30</sup> FHP individuals also respond differently to alcohol-related cues. Specifically, FHP female social drinkers have increased salivary response,<sup>31</sup> and FHP individuals have increased activity in medial prefrontal cortex (PFC), posterior cingulate, orbitofrontal, and inferior temporal cortices,<sup>32,33</sup> fusiform gyrus,<sup>34</sup> and hippocampus<sup>34</sup> in response to a variety of alcohol-related cues. Even in college samples, where FHP and FHN participants' rates of alcohol consumption are similar, FHP participants experienced more AUD symptoms, drug involvement, hangovers, and other alcohol-related problems.<sup>35</sup> Taken together, the familial transmission of AUD may be partly driven by FHP individuals' alcohol-related expectancies and altered responsivity to its biphasic effects.

**Marijuana.** In cannabis use disorder probands, 36% of first-degree relatives had AUD, which is remarkably similar to the rate of AUDs among relatives of probands with an AUD (35.5%).<sup>7</sup> This is in contrast to probands with opioid, cocaine, or without drug use disorders, for whom 14.5% to 18.1% of relatives had AUDs. These findings indicate that these two SUDs are more strongly correlated than other SUDs.<sup>7</sup> Additionally, when FHP subjects were challenged with IV  $\Delta^9$ -tetrahydrocannabinol (THC), they reported feeling more "high" than did subjects in the FHN group. However, FHP participants did not exhibit increased cognitive or physical effects in response to cannabis.<sup>36</sup> This study suggests that the cannabinoid receptor (CB1R), through which  $\Delta^9$ -THC produces its central effects, may be linked to the heritability of AUDs.<sup>36</sup> Further research examining the relationship between cannabis response and family history of AUD is warranted.

**Other substances.** FHP adults with AUD may respond better to the mu-opioid receptor antagonist naltrexone, a United States Food and Drug Administration (FDA)-approved treatment for AUD.<sup>37</sup> In FHP nontreatment seeking, alcohol-dependent adult males, pretreatment with one dose of naltrexone (100 mg) reduced the number of drinks selected during a task in which participants were given the choice to select money or alcohol.

This suggests altered opioid receptor responsivity in FHP males.<sup>37</sup> Additionally, FHP adults reported more negative subjective effects such as anxiety, distrust, and dizziness in response to IV amphetamine challenge.<sup>10</sup> Because amphetamines produce euphoric effects primarily through dopaminergic neurotransmission, increased dopamine receptor availability in FHP individuals may contribute to this increase in unpleasant effects with amphetamines.<sup>10</sup> Even preferences for sugar have been linked to family history of AUD. FHP participants are more than twice as likely to have a "sweet tooth" than FHN individuals,<sup>38</sup> and FHP participants demonstrate greater activation in the right amygdala in response to oral sucrose.<sup>39</sup>

**Ketamine.** Ketamine is a glutamate modulator and an FDA-approved dissociative anesthetic,<sup>40</sup> and the FDA has recently approved esketamine for the treatment of resistant depression (TRD).<sup>41</sup> Ketamine is a derivative of phencyclidine (PCP), which was synthetically developed to provide a less psychotomimetic alternative for anesthesia.<sup>42</sup> Ketamine and its metabolites are central nervous system penetrant, and the parent racemic compound has a relatively short half-life. Ketamine is metabolized in the liver by cytochromes (CYP) 3A and 2B6.<sup>42</sup> Because of extensive first-pass metabolism by the liver, oral ketamine has poor bioavailability. Thus, nonparenteral—intranasal, intramuscular, and IV—forms are the preferred means of administration. Ketamine is a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors.<sup>42</sup> Interestingly, subanesthetic doses of ketamine do not have an affinity for gamma-aminobutyric acid receptors in the human brain, which is unlike most other analgesics.<sup>42</sup> In higher doses, ketamine produces a trance-like dissociative state and acts as an anesthetic. In lower doses, it can relieve pain, is sedative, and can have mild psychotomimetic effects. Because of its transient hallucinogenic and tranquilizing effects, ketamine is often abused recreationally.<sup>42,43</sup> In studies that used subanesthetic doses of ketamine for TRD participants, shortly after one dose of ketamine, norketamine, dehydronorketamine, and hydroxynorketamine (Hnk) were the primary metabolites present in blood plasma.<sup>43</sup> In mice studies, ketamine, norketamine, and Hnk metabolites reached peak concentrations in the brain minutes after IV ketamine infusion.<sup>43</sup> These metabolites and their quick penetration of the blood-brain barrier may be responsible for ketamine's neuropsychiatric effects.

Not everyone has the same response to ketamine. Specifically, FHP individuals display a differential response to ketamine (Table 1) as well as other NMDA receptor antagonists such as memantine.<sup>44,45</sup> FHP participants exhibited decreased psychotomimetic effects in response to ketamine, whereas FHN participants reported greater dysphoria, negative symptoms

**Table 1.** Differential effects of ketamine based on family history of alcohol use disorders.

	Study	Population	Findings
Psychotomimetic and dissociative effects	Petrakis et al. (2004) <sup>44</sup>	Healthy subjects	FHP experienced ↓ perceptual alterations.
	Luckenbaugh et al. (2012) <sup>46</sup>	TR BD	FHP experienced ↓ dissociative effects.
Reward valence	Petrakis et al. (2004) <sup>44</sup>	Healthy subjects	FHP experienced ↓ dysphoric symptoms.
	Phelps et al. (2009) <sup>47</sup>	TR MDD	FHP experienced ↓ dysphoric symptoms.
	Yoon et al. (2016) <sup>95</sup>	Healthy subjects	FHP reported ↑ ratio stimulant (rewarding): sedative (aversive) affects.
Antidepressant response	Phelps et al. (2009) <sup>47</sup>	TR MDD	FHP had ↑ improvement of depressive symptoms 230-minutes post-infusion.
	Luckenbaugh et al. (2012) <sup>46</sup>	TR BD	FHP had ↑ improvement of depressive symptoms for three days post-infusion.
	Permoda-Osip et al. (2014) <sup>51</sup>	TR BD	FHP had ↑ improvement of depressive symptoms 14 days post-infusion; 76% of FHP were responders versus 36% of FHN.
	Niciu et al. (2014) <sup>48</sup>	TR BD and MDD	FHP had ↑ improvement of depressive symptoms one and seven days post-infusion.
	Niciu et al. (2014) <sup>49</sup>	TR MDD	FHP had ↑ depression improvement and decreased relapse for up to four weeks.
	Pennybaker et al. (2017) <sup>50</sup>	TR BD and MDD	All extended responders (four weeks post infusion) were FHP.
	Rong et al. (2018) <sup>96</sup> (systematic review)	TR BD and MDD	FHP status was the most replicated predictor of antidepressant response.

Note. FHP: family history positive; TR: treatment resistant; BD: bipolar disorder/depression; MDD: major depressive disorder, FHN: family history negative.

(e.g. psychomotor retardation and blunted affect), and dissociation.<sup>44</sup> Because both alcohol and ketamine are weak NMDA receptor antagonists, these findings suggest that aberrant NMDA receptor functioning may have a role in the transmission and development of AUDs.<sup>44</sup> Ketamine also has rapid-acting antidepressant effects in TRD and treatment-resistant bipolar disorder when administered at subanesthetic doses. Based on the differential profile described above, family history of AUD was studied as a potential predictor of treatment response with consistent demonstration of greater magnitude and maintenance of antidepressant efficacy in FHP unipolar and bipolar TRD subjects.<sup>46–51</sup> Table 1 provides an overview of research findings regarding differential response to ketamine in FHP individuals.

Our group is currently using a multimodal approach (including pharmacological imaging) to identify alcohol-sensitive biomarkers of antidepressant response to ketamine (Clinicaltrials.gov ID: NCT02122562). Many FHP neuroanatomical and neurocognitive correlates have been identified to date, and, we hypothesize, some may relate to antidepressant response to ketamine. We will now turn to these structural and functional differences.

### FHP Neuroanatomical and Neurocognitive Correlates

Tessner and Hill<sup>52</sup> reviewed the neural circuitry associated with risk factors for developing AUD, which

they conceived as consisting of both internalizing and externalizing pathways. The externalizing pathway consists of altered cerebellothalamocortical circuitry and is characterized by behavioral disinhibition. The internalizing pathway, on the other hand, is characterized by aberrant reward sensitivity. The amygdala, nucleus accumbens (NAcc), hypothalamus, cingulate, and orbito-frontal cortex are implicated in the internalizing pathway.<sup>52</sup> Our review supports these pathways, as altered amygdala, NAcc, cortical, and cerebellar structure and function are frequently reported in FHP participants. Additionally, neurocognitive differences associated with FHP, such as altered reward-sensitivity, impulsivity, and executive functioning, are typically associated with altered activation in these brain areas. We will now review structural brain differences in FHP individuals.

### Neuroanatomical Differences

Magnetic resonance imaging (MRI) and functional MRI (fMRI) are commonly used methods for studying structural and functional brain differences, respectively, between FHP and FHN individuals. These neuroimaging modalities have identified differences in several brain structures including the amygdala, basal ganglia, neocortex, cerebellum, and hippocampus (Table 2).



**Table 2.** Neuroanatomical and molecular differences based on family history of alcohol use disorders.

Structure	Studies	Findings
Amygdala	Hill et al. (2013) <sup>53</sup> ; Dager et al. (2014) <sup>9</sup>	FHP adults and adolescents have ↓ amygdala volumes.
	Benegal et al. (2007) <sup>54</sup> ; Hill et al. (2001) <sup>15</sup>	FHP adults and children have ↓ right amygdala volumes.
	Sjoerds et al. (2013) <sup>56</sup>	No volume differences in adult sample.
	McHugh et al. (2010) <sup>55</sup>	FHP children with short allele 5-HTTLPR have smallest amygdala.
	Cservenka et al. (2015) <sup>58</sup>	↑ FH density was related to ↑ NAcc volumes in adolescent females, not in males.
Basal ganglia	Squeglia et al. (2014) <sup>17</sup>	No differences in NAcc volume in youth sample.
	Dager et al. (2014) <sup>9</sup> ; Hill et al. (2013) <sup>53</sup> ; Benegal et al. (2007) <sup>54</sup>	No volume differences in the putamen, caudate, or globus pallidus.
	Alvanzo et al. (2017) <sup>10</sup>	FHP adults have ↑ dopamine receptor availability in posterior caudate, anterior putamen, and right ventral striatum.
	Benegal et al. (2007) <sup>54</sup>	FHP adolescents had ↓ cingulate and superior frontal gyrus volumes.
	Sjoerds et al. (2013) <sup>56</sup> ; Dager et al. (2014) <sup>9</sup>	No volume differences were found in adult sample.
Neocortex	Cohen-Gilbert et al. (2015) <sup>61</sup>	FHP adolescents had ↑ glutamine/glutamate ratio in anterior cingulate cortex. This was not found in adults.
	Jones and Nagel (2019) <sup>65</sup>	FHP youth had ↓ FA in prefrontal cortex and ↓ MD in thalamus. This affect dissipated by late adolescence.
	Acheson et al. (2014) <sup>64</sup>	FHP youths had ↓ FA in frontocortical areas.
Cerebellum	Hill et al. (2007) <sup>66</sup> ; Benegal et al. (2007) <sup>54</sup>	FHP male youth and adults had ↑ gray matter volumes in cerebellum than FHN males.
	Hill et al. (2011) <sup>67</sup> ; Hill et al. (2016) <sup>68</sup>	FHP adolescents and adults had ↑ cerebellar volumes.
	Cardenas et al. (2005) <sup>70</sup>	FHP heavy drinkers lost ↓ gray and white matter volume due to chronic alcohol use than FHN heavy drinkers.
	Benegal et al. (2007) <sup>54</sup>	FHP participants had ↓ hippocampal volume.
Hippocampus	Benegal et al. (2007) <sup>54</sup> ; Sjoerds et al. (2013) <sup>56</sup>	FHP participants had ↓ parahippocampal gyrus volume.
	Hanson et al. (2010) <sup>71</sup>	FHP adolescent males had ↑ left hippocampal volume than FHN males. No differences in adolescent females.
	Dager et al. (2014) <sup>9</sup> ; Hill et al. (2001) <sup>15</sup>	No volume differences.

Note. FHP: family history positive; FH: family history; NAcc: nucleus accumbens; FA: fractional anisotropy; MD: mean diffusivity; FHN: family history negative.

**Amygdala.** One of the most well-replicated neuroimaging findings in FHP individuals is abnormal amygdala volume. Several studies have found that FHP individuals have smaller amygdala than FHN individuals,<sup>9,53</sup> whereas other studies found this difference only in the right amygdala.<sup>15,54</sup> Smaller amygdala have been detected as early as childhood<sup>54</sup> and persist after matching for IQ and socioeconomic status.<sup>15</sup> Genetic research links family history with amygdala volume. HR children who carry the short allele of 5-HTTLPR, a serotonin transporter gene implicated in alcohol dependence risk,<sup>55</sup> had the smallest amygdala volumes compared to long allele and LR counterparts.<sup>53</sup> The authors hypothesized that

smaller amygdala volumes are a result of stressful childhood experiences, as family cohesion predicted larger amygdalas, and that those who had short alleles were most vulnerable to environmental influences.<sup>53</sup> However, some evidence suggests that smaller amygdala volumes are the result of a developmental lag rather than a static difference between FHP and FHN individuals. Sjoerds et al.<sup>56</sup> found no differences in amygdala volumes in an adult sample, and Benegal et al.<sup>54</sup> found that family history-related brain differences were most prominent in the younger participants in the study. Given that most studies that identified differences in amygdala volume examined adolescents and emerging adults,<sup>15,53,54</sup>

longitudinal research is needed to determine if the amygdala shows a different pattern of development in FHP versus FHN individuals and whether stressful experiences, rather than FHP, are a better predictor of amygdala volumes. Smaller amygdalas are related to increased aggression in adulthood<sup>57</sup>; however, it is unclear if this applies to children. Task-related fMRI research suggests the altered amygdala may lead to increased risk-taking, which will be discussed later.

**NAcc and other basal ganglia structures.** Several structures within the basal ganglia have been examined in relation to family history of AUD, with NAcc being of particular interest. Greater FH density has been linked to increased NAcc volumes in adolescent, alcohol-naive females but not males;<sup>58</sup> however, other studies have demonstrated no differences in NAcc volumes.<sup>17</sup> Because the NAcc is associated with reward reactivity, possible volumetric differences in females may indicate altered responsiveness to rewards. While volumetric differences in other basal ganglia structures such as the caudate,<sup>9,53,54</sup> globus pallidus,<sup>9</sup> or putamen<sup>9</sup> have not been found, differences in dopamine receptor availability between FHP and FHN individuals have been identified. Specifically, FHP non-alcohol-dependent adult drinkers have more dopamine (D<sub>2</sub>/D<sub>3</sub>) receptor availability in the right ventral striatum, posterior caudate, and anterior putamen (areas associated with reward and motivation) than their FHN counterparts.<sup>10</sup> Because these results were obtained from an adult sample of drinkers who had not developed an AUD despite elevated risk, the increased dopamine (D<sub>2</sub>/D<sub>3</sub>) receptor availability in basal ganglia structures may be a protective factor against developing an AUD for FHP individuals.

**Neocortex.** Cortical differences between FHP and FHN individuals have been examined using a variety of neuroimaging techniques including MRI, fMRI, and magnetic resonance spectroscopy (MRS). A number of cortical regions are smaller in FHP youth, i.e., smaller cingulate, superior frontal gyrus (SFG), and thalamic volumes,<sup>54</sup> but not FHP adults.<sup>9,56</sup> Furthermore, FHP alcohol-naive adolescents had thinner cortices in frontal and parietal lobes when compared to FHN adolescents, which was more pronounced at younger ages.<sup>59</sup> Reduced volumes in cortical areas are associated with increased externalizing symptoms, which may contribute to the development of AUD and other negative outcomes.<sup>54</sup> These findings in FHP youths, which have not been replicated with adults, could again support a developmental lag hypothesis, which is described in great detail below. It is also possible that many older FHP adolescents with significant alcohol use were excluded from this study, resulting in a biased group of older FHPs.<sup>59</sup>

MRS utilizes the signal shift from hydrogen ions (protons) to determine concentrations of metabolites in a

specific tissue, including the brain.<sup>60</sup> Commonly examined neurometabolites include N-acetyl aspartate, lipids, lactate, and glutamine/glutamate.<sup>60</sup> Using MRS, researchers have found that FHP adolescents, but not FHP adults, have elevated glutamine/glutamate ratios in the anterior cingulate cortex compared to FHN adolescents.<sup>61</sup> Interestingly, FHP adolescents had glutamine/glutamate ratios that were *more* similar to both FHN and FHP adults.<sup>61</sup> In FHP adults, increased motor impulsivity was associated with lower glutamine/glutamate ratios, whereas in FHN adolescents, increased impulsivity was associated with higher glutamine/glutamate ratios.<sup>61</sup> These results suggest that altered glutamine/glutamate ratios may be related to impulsivity in FHP participants.

Another neuroimaging technique, diffusion tensor imaging, allows researchers to measure white matter integrity by measuring mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity, and radial diffusivity.<sup>62</sup> FA measures directionality of water diffusion. Greater FA indicates more organized and greater white matter integrity.<sup>63</sup> MD measures magnitude of water diffusion, which also provides insights into the integrity of white matter microstructure.<sup>63</sup> FHP youths have been reported to have lower FA in frontocortical areas, indicating poorer white matter integrity,<sup>64</sup> and increased impulsivity due to decreased top-down control of subcortical brain regions, i.e., amygdala. However, another study found that FHP youth have *higher* FA in 19 white matter regions.<sup>17</sup> A recent longitudinal study followed FHP individuals through adolescence and compared those who went on to become binge drinkers versus those who did not.<sup>65</sup> FHP was related to reduced FA in the PFC and reduced MD in the thalamus,<sup>65</sup> but these differences dissipated by late adolescence.<sup>65</sup> This indicates white matter integrity may also be affected by a proposed developmental delay. They also found that FHP adolescents who went on to binge-drink had lower MD in the SFG *before* the onset of binge drinking, compared to FHP counterparts that did not go on to binge-drink.<sup>65</sup> This indicates that lower MD in cortical areas in FHP adolescents is related to greater risk of problematic alcohol use, although this effect may not persist into adulthood.

**Cerebellum.** Several studies have examined the cerebellum as it relates to family history of AUD, with variable results. For example, HR male adolescents and young adults have greater gray matter volumes in the right cerebellum compared to their LR counterparts.<sup>66</sup> A subsequent study from the same group reported that HR adolescents and young adults had greater gray matter volume and total volume in the cerebellum but found no significant differences in *white* matter volumes.<sup>67</sup> A more recent study found that HR adolescents and young adults had greater gray matter, white matter, and total cerebellar volumes.<sup>68</sup> In contrast,

Benegal et al.<sup>54</sup> reported that HR male youth (ages 8–24) had *smaller* gray matter volumes compared to FHN individuals. Notably, there are discrepancies between the Hill et al.<sup>66,67</sup> studies and Benegal et al.'s study that may explain these contrasting results. Namely, Benegal et al.<sup>54</sup> used an alcohol-naïve sample, whereas the Hill et al.<sup>66–68</sup> studies included participants that were not alcohol-naïve, with some participants meeting criteria for an AUD or other SUDs. While it is unclear the nature of the relationship between cerebellar volumes and FHP youth, abnormalities may translate to altered motor abilities.

Ultimately, it may be difficult to tease out the effects of familial risk versus alcohol consumption in young adult and older populations, as alcohol consumption is also related to decreased cerebellar volume,<sup>69</sup> and family history of AUD is associated with greater alcohol consumption and increased risk of AUD. Specifically, FHP heavy drinkers had lower cerebrospinal fluid volumes than FHN heavy drinkers, indicating FHP heavy drinkers had lost *less* gray and white matter volume due to chronic alcohol abuse than did FHN heavy drinkers. In short, FHP status was a protective factor against gray and white matter losses due to chronic alcohol abuse.<sup>70</sup> As a result, age of first drink, past and/or recent alcohol consumption, AUD diagnosis, and potentially other drinking-related variables should be entered as covariates in future studies of the effects of family history of AUD on cerebellar volume.

**Hippocampus.** The hippocampus has also been a region of interest when examining differences between FHP and FHN individuals, and, as in the cerebellum, results have been variable. FHP participants had smaller hippocampi<sup>54</sup> and smaller surrounding structures, i.e., smaller parahippocampal gyrus, than their FHN counterparts.<sup>54,56</sup> However, other studies have found that FHP adolescent males had *larger* left hippocampi than their male FHN counterparts with no hippocampal volume differences observed in adolescent females.<sup>71</sup> Other studies found no differences in hippocampal volumes between FHP and FHN participants.<sup>9,15</sup>

While further research is needed to verify the relationship between FHP and the hippocampus, altered volume in this area may relate to altered behavioral inhibition and visual-spatial functioning related to FHP, which will be discussed in depth later in the paper. While several studies have linked alcohol use to reduced hippocampal volumes,<sup>72</sup> further research is necessary to determine how much reduced volume, if any, can be attributed to family history of AUD.

In sum, numerous neuroimaging modalities have been used to study and identify structural, functional, and neurochemical differences between FHP and FHN individuals. Structural differences between FHP and FHN

seem to be more common in youth than in adults. This alludes to the proposed neurodevelopmental lag in FHP individuals, i.e., brain structure and/or function is developmentally aberrant (“behind”) in childhood and/or adolescence, but, by the time FHP individuals reach adulthood, these differences are no longer apparent (“caught up”) compared to their age-matched FHN counterparts. However, in order to separate the effects of alcohol use from effects of familial risk, many studies include only alcohol-naïve or nonalcohol-dependent participants. In contrast to the neurodevelopmental lag hypothesis, it may also be possible that, by adulthood, many FHP individuals have succumbed to AUD and are excluded from these studies, thereby contributing to sampling bias, i.e., resilient FHP participants who more closely resemble FHN subjects in adulthood.

Next, even in the most commonly studied brain regions, there are contradictory neuroanatomical findings. In addition to possible sampling biases and age-related effects, many studies have small samples that are underpowered to detect small-to-moderate effects. The use of disparate neuroimaging platforms, processing pipelines, and result interpretation may also muddle the water. Nevertheless, given the number of structural and functional brain differences in FHP and FHN groups that have been reported, one would also anticipate altered neurocognitive performance and traits. We will now review the research examining neurocognitive differences based on family history of AUD.

### Neurocognitive Differences

Many studies have examined family history of AUD in relation to neurocognitive performance using a variety of self-reported and task performance measures (Table 3). While many aspects of neurocognition have been studied, executive functioning differences between FHP and FHN individuals have been the most extensively studied. Executive function includes a number of higher order cognitive tasks including inhibition, motivation, working memory, spatial performance, emotional regulation, and attention-shifting, which will each be described sequentially.<sup>73</sup>

**Inhibition.** Family history of AUD is related to increased impulsivity<sup>59,74–76</sup> based on task performance and self-report; however, as is the case in the neuroanatomy literature, not every study has replicated these findings.<sup>77–79</sup> Although participants did not perform or rate themselves differently on impulsiveness, FHP participants displayed greater activation in the posterior cingulate/precuneus, bilateral middle/superior temporal gyrus, and medial SFG while performing impulsivity tasks,<sup>80</sup> and FHP males displayed greater activation in the left insula and interior frontal gyrus during a similar

**Table 3.** Neurocognitive differences based on family history of alcohol use disorders.

Structure	Studies	Findings
Inhibition	Acheson et al. (2014) <sup>80</sup>	FHP youths had ↑ activation in posterior cingulate/precuneus, bilateral middle and superior temporal gyrus, and medial superior FG during Go/NoGo task. FHP youths had slower reaction times.
	DeVito et al. (2013) <sup>81</sup>	FHP adults had ↑ activation in left anterior insula and inferior FG during Go/NoGo task.
	Henderson et al. (2018) <sup>59</sup>	FHP adolescents had ↑ scores on delay discounting task.
	Gierski et al. (2013) <sup>75</sup>	FHP adults had ↓ performance on Wisconsin Card Sorting Task and Stroop test. FHP adults rated themselves as more impulsive.
Motivation	Acheson et al. (2011) <sup>76</sup>	FHP adults had ↓ performance on GoStop task.
	Andrews et al. (2011) <sup>77</sup>	FHP participants had ↑ activity in caudate at prospect of reward, ↓ activity in NAcc, insula, and orbitofrontal cortex when anticipating reward, and ↓ activity in NAcc and amygdala after loss.
	Acheson et al. (2009) <sup>79</sup>	FHP participants had ↑ activity in the left dorsal anterior cingulate cortex and left caudate nucleus during Iowa Gambling Task.
	Cservenka and Nagel (2012) <sup>85</sup>	FHP adolescents had ↓ activation in the right cerebellum and right dorsolateral PFC when making risky decisions on a task.
Working Memory and Spatial Performance	Glahn et al. (2007) <sup>83</sup>	FHP participants did not demonstrate amygdala activation in response to fearful faces, whereas FHN participants did.
	Yarosh et al. (2014) <sup>74</sup>	FHP participants rated themselves as ↑ reward-sensitive.
	Cservenka et al. (2012) <sup>86</sup>	FHP youth had slower reaction times on a verbal working memory task. They had ↓ activation in the right anterior and dorsolateral PFCs, right cingulate gyrus, and right inferior FG during said task.
	Henderson et al. (2018) <sup>59</sup>	FHP adolescents had ↓ performance on visual spatial sequence task.
	Acheson et al. (2011) <sup>76</sup>	FHP adults had ↓ performance on immediate memory task.
	Corral et al. (2003) <sup>90</sup>	FHP subjects ages 7 to 15 had ↓ scores on block design and digit span. These effects dissipated by the time participants were ages 11 to 17.
	Garland et al. (1993) <sup>16</sup>	FHP males took more trials to learn how to perform a spatial task.

Note. FHP: family history positive; FG: frontal gyrus; NAcc: nucleus accumbens; PFC: prefrontal cortex; FHN: family history negative.

impulsivity task.<sup>81</sup> This indicates that, while there may not always be observable differences in behavior, inhibitory control may require more cognitive effort for FHP individuals. FHP individuals requiring more cognitive effort may suggest some sort of detrimental deficit. However, increased activation in the dorsolateral PFC during correct No-Go trials on a Go/No-Go task predicted resilience against substance use for FHP youth.<sup>82</sup> More research is necessary in order to determine what differences in activation might mean for long-term outcomes.

**Motivation.** FHP individuals are more consistently motivated by rewards.<sup>59,76,74</sup> FHP participants had greater activation in the left dorsal anterior cingulate cortex and left caudate nucleus during a gambling task.<sup>79</sup>

FHP participants demonstrated greater activation in the caudate at the prospect of a monetary reward, less activation in the insula, orbitofrontal cortex, and NAcc<sup>77</sup> at the anticipation of reward, and decreased activation in the NAcc and amygdala<sup>77</sup> when failing to win money, thereby indicating that FHP participants may be less sensitive to monetary loss. Additionally, FHP young adults have decreased amygdala activation in response to fearful faces compared to their FHN counterparts, indicating FHP individuals may be less fearful and less likely to develop risk aversion.<sup>83</sup> Furthermore, FHP adolescents demonstrated an attenuated emotion-modulated startle response in comparison to their FHN counterparts.<sup>84</sup> Similarly, while no differences were observed on risk-taking behaviors in decision-making tasks,<sup>85,79</sup> FHP participants demonstrated less activation in the right



cerebellum when making risky decisions compared to their FHN counterparts,<sup>85</sup> again suggesting that FHP participants are less risk responsive.

**Working memory and spatial performance.** FHP individuals also perform differently on working memory tasks.<sup>86–88</sup> For example, FHP youth had slower reaction times on a verbal working memory task and reduced activity in the PFC during said task.<sup>86</sup> Similarly, FHP was related to decreased activation in the right cerebellum during a spatial working memory task; however, there were no FHN versus FHP group performance differences.<sup>87</sup> FHP youth have demonstrated reduced connectivity between contralateral cerebellar regions and anterior PFC, independent of task-related activation.<sup>89</sup> This altered activation and connectivity may explain FHP individual's altered responses to visuospatial tasks in some studies.<sup>13,16,59</sup> Specifically, FHP males took more trials to learn how to perform a spatial task than FHN males.<sup>16</sup> In another study, 7- to 15-year-old FHP children had lower scores with block design and digit span; however, three years later, in the same cohort (now 11–17 years old), there were no observable group differences,<sup>90</sup> thereby fitting the aforementioned neurodevelopmental lag hypothesis in FHP youth and adolescents.

**Other.** A number of other neurocognitive differences have been found. Namely, FHP individuals may have difficulty with shifting attention<sup>75</sup> and emotional regulation.<sup>84</sup> They may also experience more negative affect and poorer mood regulation than FHN individuals.<sup>91</sup> Being FHP was related to increased early life adversity, which also predicted poorer mood regulation and negative affect.<sup>91</sup>

Taken together, a family history of AUD has been linked to altered performance on various neurocognitive tasks. Specifically, FHP participants are more impulsive, variably reward-responsive, less risk and loss-averse, and have altered activity and performance on working and spatial memory tasks that, in many cases, predate the development of alcohol problems.

## Conclusion

Family history of AUD has been multimodally studied for several decades, and it is safe to say is related to much more than simply increased risk of alcoholism. In imaging studies, FHP individuals demonstrate differences in brain volumes, activity, connectivity, and neurochemistry, as well as increased impulsivity and reward sensitivity. A re-occurring theme throughout the literature is that FHP youth, but not adults, are much more likely to demonstrate volumetric differences across several brain

regions. Although the neurotoxic effects of alcohol may be at play in young drinkers, the extant literature suggests that FHP may be associated with a neurodevelopmental lag in brain maturation. Currently, there is no direct outcome data on this hypothesized neurodevelopmental lag in FHP participants. One study has linked childhood neural activity in FHP youth to resiliency in adulthood,<sup>82</sup> which indicates that neurodevelopmental differences in FHP children may affect later outcomes. Interestingly, there is significant overlap between altered brain structures associated with FHP and brain structures associated with Attention Deficit-Hyperactivity Disorder (ADHD), including the cerebellum, basal ganglia, and PFC,<sup>92</sup> and a similar phenomenon of neurodevelopmental delay has been reported in ADHD youth. Brain networks associated with ADHD symptoms demonstrated a developmental lag in ADHD children, with the most severe presentations being associated with increasing delay.<sup>93</sup> While there is no research on how a neurodevelopmental lag directly affects ADHD children, a childhood ADHD diagnosis is associated with long-term adverse outcomes, i.e., unemployment.<sup>94</sup>

In addition to neuroanatomical, neurophysiological, and psychological differences at baseline, FHP subjects also respond differently to numerous substances including alcohol and ketamine. FHP adults are more sensitive to alcohol's stimulant (ascending limb) effects while simultaneously being less sensitive to its sedative (descending limb) effects. FHP individuals also demonstrate altered brain activity to alcohol-related cues and experience more detrimental outcomes, such as hangovers, from drinking even when consumption levels are similar. After alcohol, ketamine has been the most studied drug in FHP subjects, demonstrating attenuated dissociative, psychotomimetic, and acute dysphoric reactions during administration and, in FHP TRD, greater magnitude and maintenance of antidepressant efficacy to subanesthetic dose infusion.

Lastly, future research is warranted across numerous domains. Although neuroimaging findings are consistent with the developmental lag hypothesis, large sample, longitudinal studies are needed to more properly examine differential brain developmental trajectories. Additionally, more research is needed to investigate various risk and protective factors in FHP individuals, in order to remediate risks and promote resiliency. More research is also needed to understand the neurobiology of altered antidepressant response to subanesthetic dose ketamine based on family history of AUD. The knowledge gained by this research may assist prescribers to better predict which patients may have an augmented and even exceptional antidepressant response to ketamine and potentially other glutamate-based interventions in a "precision psychiatry" treatment framework.

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