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Family History Of Alcohol Use Disorder As A Predictor Of Endogenous Pain Modulatory Function

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Abstract

Family history of alcohol use disorder (AUD) is frequently endorsed by chronic pain patients. Although individuals with a family history of AUD have demonstrated enhanced sensitivity to painful stimulation, we are not aware of any previous research that has examined clinically-relevant endogenous pain modulation (i.e., capacity to inhibit or facilitate pain) in this population. The goal of this study was to test family history of AUD as a predictor of conditioned pain modulation, offset analgesia, and temporal summation among a sample of moderate-to-heavy drinkers. Participants ($N = 235$; 58.3% male; $M_{age} = 34.3$, $SD = 12.3$) were evaluated for family history of AUD at baseline (family history positive: $n = 54$; 59.3% white) and pain modulatory outcomes were assessed via quantitative sensory testing. Results indicated that participants with a family history of AUD (relative to those without) evinced a pro-nociceptive pain modulation profile in response to experimental pain. Specifically, family history of AUD was associated with deficits in pain-inhibitory processes, which may help to explain the observed high rates of familial AUD in chronic pain patients. Exploratory analyses further suggested these effects may be driven by paternal AUD. The current findings suggest a family history of AUD may confer risk for AUD *and* chronic pain. Clinically, these data may inform treatment decisions for acute pain among individuals with a family history of AUD.

Keywords: family history, alcohol use disorder, endogenous pain modulation

Family History of Alcohol Use Disorder as a Predictor of Endogenous Pain Modulatory Function

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Chronic pain is a significant and impactful condition, affecting an estimated 50 million U.S. adults (Dahlhamer et al., 2018) with costs in excess of $600 billion each year in healthcare expenses and lost productivity (Gaskin & Richard, 2012). Dysfunction in capacity to inhibit or facilitate pain (i.e., endogenous pain modulation) has been identified as an important mechanism in the development of chronically painful conditions (Ossipov, Morimura, & Porreca, 2014; van Wijk & Veldhuijzen, 2010; Yarnitsky, 2015), and individuals living with idiopathic pain syndromes (e.g., fibromyalgia, irritable bowel syndrome, temporomandibular disorder, etc.) have consistently demonstrated such dysfunction (Heymen et al., 2010; Kosek & Hansson, 1997; Maixner, Fillingim, Sigurdsson, Kincaid, & Silva, 1998). Pre-operative endogenous pain modulatory function among pain-free patients has also been shown to predict the incidence and severity of chronic post-operative pain (Wilder-Smith, Schreyer, Scheffer, & Arendt-Nielsen, 2010; Yarnitsky et al., 2008). Thus, the capacity to modulate experimental pain has important bearing on chronic pain susceptibility, even among those currently unencumbered by pain. Although these prospective findings suggest a pathophysiological role for abnormal endogenous pain modulation in the development of chronic pain, factors that predispose individuals to differential pain modulatory function remain largely understudied. The current study is the first to examine family history of alcohol use disorder (AUD) as a predictor of endogenous pain modulation.

Alcohol Use as a Risk Factor for Chronic Pain

The consumption of alcohol is known to confer acute analgesia (Thompson, Oram, Correll, Tsermentseli, & Stubbs, 2017). However, alcohol use may promote increased pain over time. For example, long-term heavy alcohol use has been established as a causative factor in the

onset of chronically painful conditions such as pancreatitis and alcohol neuropathy (Apte & Wilson, 2003; Sadowski & Houck, 2019). Chronic pain, often defined as pain that persists or recurs for more than three months (Treede et al., 2019), is also frequently observed in individuals seeking treatment for AUD (e.g., Boissoneault, Lewis, & Nixon, 2019; Sheu et al., 2008), with up to 73% endorsing moderate-to-severe past-month pain (Larson et al., 2007). Nationally representative longitudinal data further indicates that drinkers who ceased alcohol consumption over a three-year follow-up period demonstrated reduced bodily pain at the subsequent wave (Imtiaz, Loheswaran, Le Foll, & Rehm, 2018).

Long-term heavy alcohol use may contribute to negative pain outcomes via several pathways. Egli, Koob, and Edwards (2012) detailed evidence that alcohol dependence and chronic pain share overlapping neural substrates and proposed an allostatic load model in which repeated episodes of alcohol intoxication/withdrawal may result in pathological changes to reward and stress circuitry. This model suggests long-term heavy alcohol exposure may give rise to chronic pain, in part, through dysregulation of opioid systems involved with endogenous pain modulation. In contrast to acute alcohol consumption, which stimulates the release of opioid peptides (e.g., Mitchell et al., 2012), sustained heavy alcohol use is believed to result in a central opioid deficiency (Gianoulakis, 2001). Alcohol is also known to interact with several other neurotransmitter systems involved in endogenous pain modulation, including glutamate, GABA, and serotonin (Chastain, 2006; Ossipov, Dussor, & Porreca, 2010).

Endogenous Pain Modulation

Endogenous pain modulation is a broad term that encompasses the ways in which the central nervous system can inhibit or facilitate pain. The brain exerts bi-directional control of pain via descending inhibitory and facilitatory mechanisms that can reduce or enhance

nociceptive signals (i.e., those pertaining to actual or potential tissue damage; IASP, 2008), primarily at the level of the spinal cord (Ossipov et al., 2010; Staud, 2013). Following injury or repeated noxious stimulation, secondary neurons in the dorsal horn can also undergo central sensitization (Latremoliere & Woolf, 2009), which is characterized as increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input (IASP, 2008). Preclinical evidence suggests that disruption of the inhibitory-facilitatory balance may lead to an enhanced pain state if facilitation predominates (e.g., Pertovaara, 1998). However, an efficient pain inhibitory system can protect against the manifestation of an enhanced pain state (e.g., Xu, Kontinen, & Kalso, 1999).

In humans, quantitative sensory testing (QST) is a gold-standard approach to examining intermediate phenotypes relevant to chronic pain (Diatchenko, Fillingim, Smith, & Maixner, 2013). QST is a psychophysical test methodology that can assess sensory nervous system function and identify deviations in pain perception and modulation (Diatchenko et al., 2013; Roldan & Abdi, 2015). Indeed, a number of dynamic test paradigms have been developed to activate and quantify pain inhibitory and facilitatory mechanisms. Assessment of both mechanisms enables characterization of individual pain modulation profiles, such that low-efficiency inhibition and/or enhanced facilitation would indicate a pro-nociceptive profile, and efficient inhibition and/or unenhanced facilitation would indicate an anti-nociceptive profile (Yarnitsky, Granot, & Granovsky, 2014). Individuals with a pro-nociceptive pain modulation profile may therefore experience more severe pain and have a higher probability of developing chronic pain, relative to those with an anti-nociceptive pain modulation profile (Yarnitsky et al., 2014). QST paradigms commonly used to establish pain modulation profiles include conditioned pain modulation (CPM), offset analgesia (OA), and temporal summation (TS).

Conditioned pain modulation. CPM is a dynamic test paradigm used to assess a central mechanism that inhibits pain (Le Bars, Dickenson, & Besson, 1979a, 1979b; Yarnitsky, 2010). CPM is demonstrated through the reduction of pain ratings to a noxious experimental stimulus by application of a remote conditioning stimulus. This process has been described as a "pain inhibits pain" phenomenon and is mediated by spino-bulbo-spinal loops and higher-order cerebral mechanisms (Le Bars et al., 1979a, 1979b; Leone & Truini, 2019). Deficits in CPM efficiency have been observed in numerous chronic pain conditions, especially idiopathic pain syndromes (e.g., Heymen et al., 2010; King et al., 2009; Leonard et al., 2009; Potvin et al., 2010). In an attempt to clarify whether reduced CPM efficiency was a causative factor or consequence of chronic pain, Yarnitsky and colleagues (2008) assessed CPM in pain-free patients prior to thoracotomy, and then evaluated chronic post-operative pain 6 - 12 months following surgery. Results indicated that CPM efficiency predicted both the incidence and severity of chronic post-operative pain (Yarnitsky et al., 2008). Similar results were demonstrated in a sample of patients receiving abdominal surgery (Wilder-Smith et al., 2010). Taken together, these findings suggest the capacity to modulate experimental pain translates directly to a clinical context, with less efficient CPM predisposing individuals to chronic pain.

Offset analgesia. OA is a dynamic test paradigm used to assess a central pain-inhibitory mechanism (Grill & Coghill, 2002). OA is demonstrated through a disproportionately large reduction in pain ratings after an incremental decrease in the intensity of a noxious stimulus, and has been characterized as a temporal contrast mechanism for nociceptive information (Grill & Coghill, 2002; Yelle, Rogers, & Coghill, 2008). Absent or reduced OA has been observed in neuropathic pain (e.g., Niesters, Hoitsma, Sarton, Aarts, & Dahan, 2011; Niesters et al., 2014) and several other chronically painful conditions (e.g., Oudejans, Smit, van Velzen, Dahan, &

Niesters, 2015; Szikszay, Adamczyk, Carvalho, May, & Luedtke, 2020). Despite both evoking pain inhibition, neuroimaging indicates that OA and CPM rely on distinct mechanisms (Nahman-Averbuch et al., 2014). For example, the OA effect has been associated with activation of brain regions supporting descending pain modulation, whereas the CPM effect has been associated with reductions in brain activity in regions involved in afferent nociceptive processing (Nahman-Averbuch et al., 2014). Moreover, OA and CPM can be differentially affected by pharmacological manipulations (e.g., opioid receptor antagonism), and preliminary evidence indicates unique relations with lifestyle factors, such as physical activity (King et al., 2013; Martucci, Eisenach, Tong, & Coghill, 2012; Naugle & Riley, 2014). Taken together, these results support the notion that OA and CPM reflect distinct features of endogenous pain inhibition (Hermans, Calders, et al., 2016).

Temporal summation. TS is a dynamic test paradigm used to assess a central mechanism that facilitates pain (Price & Dubner, 1977). TS is demonstrated through the enhancement of pain ratings along the duration of a noxious stimulus or train of noxious stimuli, despite a fixed stimulus intensity (Granot, Granovsky, Sprecher, Nir, & Yarnitsky, 2006). This process is believed to reflect summation of C-fiber-mediated responses of dorsal horn neurons (Price & Dubner, 1977; Price, Mao, Frenk, & Mayer, 1994). The TS paradigm acts as a proxy for central sensitization, which is thought to contribute to an array of chronic pain conditions (Arendt-Nielsen et al., 2018). Indeed, enhanced TS has been observed in those with post-herpetic neuralgia (e.g., Eide, Stubhaug, Bremnes, & Breivik, 1994), chronic low back pain (e.g., Owens et al., 2016), osteoarthritis (e.g., Finan et al., 2013), and fibromyalgia (e.g., Staud, Robinson, & Price, 2007), among others. Pre-operative TS in patients with osteoarthritis has also been shown to predict the development of chronic post-operative pain following knee and hip replacement

(Izumi, Petersen, Laursen, Arendt-Nielsen, & Graven-Nielsen, 2017; Petersen, Arendt-Nielsen, Simonsen, Wilder-Smith, & Laursen, 2015).

Acute Alcohol Effects on CPM

Acute analgesic properties of alcohol have long been observed (e.g., Mullin & Luckhardt, 1934). However, the effects of alcohol on clinically-relevant pain modulatory processes have received little empirical attention. Initial data indicates that acute alcohol intoxication augments CPM efficiency but has no effect on TS (Horn-Hofmann, Capito, Wolstein, & Lautenbacher, 2019), leading to the suggestion that alcohol analgesia may be a consequence of increased endogenous pain inhibition rather than reduced pain facilitation. Given the frequent endorsement of alcohol use for self-medication in the context of chronic pain (e.g., Riley & King, 2009), it has been further posited that deficient CPM may serve as a risk factor in the development of AUD among those with a greater vulnerability to pain (Horn-Hofmann et al., 2019). In the current study, we contend that a family history of AUD may also influence endogenous pain modulatory function, conferring risk for chronic pain.

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Family History of AUD

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The potential for alcohol to alter pain processing through long-term or heavy use suggests covariation between individual drinking history and pain reactivity. Consistent with this notion, men with AUD, while sober, have demonstrated greater sensitivity to painful stimulation than controls (e.g., Brown & Cutter, 1977). However, research on the pain characteristics of those with AUD may confound the effects of protracted alcohol use with the effects of premorbid factors (Stewart, Finn, & Pihl, 1995). One means of circumventing this limitation involves studying healthy individuals at risk for developing AUD, such as those with a family history of AUD (FH+). Long-standing evidence indicates that FH+ individuals are at risk for AUD by

virtue of several biopsychosocial influences, including genetics and familial modeling of drinking behavior (e.g., Cadoret, Cain, & Grove, 1980; Chipperfield & Vogel-Sprott, 1988; Cloninger, Bohman, & Sigvardsson, 1981; Dawson, Harford, & Grant, 1992).

Family History of AUD and Pain

A family history of AUD is frequently reported by individuals with chronic pain (e.g., 38% - 55%; Goldberg, Pachas, & Keith, 1999; Katon, Egan, & Miller, 1985; Pecukonis, 2004). Although there are several possible explanations for this relationship, there is reason to believe that family history of AUD may influence pain outcomes, irrespective of individual patterns of alcohol consumption. For example, FH+ individuals have demonstrated increased sensitivity to painful electrical stimulation, relative to controls with a negative family history of AUD (FH-; Stewart et al., 1995). Importantly, groups in this study were observed to be equivalent in their weekly consumption of alcohol, suggesting the heightened sensitivity to painful stimulation in FH+ individuals was more likely a premorbid factor than it was a consequence of drinking pattern (Stewart et al., 1995). The results of this investigation are consistent with research indicating that FH+ individuals have a tendency to hyper-react to environmental stressors, as indexed by cardiovascular autonomic nervous system measures, such as digital blood volume amplitude (e.g., Conrod, Pihl, & Ditto, 1995; Finn & Pihl, 1987). Indeed, the physiology underlying control of the cardiovascular system is believed to overlap with systems that modulate the perception of pain (Randich & Maixner, 1984), and the functional relationship between these systems appears to be altered in some chronic pain conditions (Bruehl & Chung, 2004; Schlereth & Birklein, 2008).

Potential Mechanisms

Measures of family history of AUD are sometimes viewed as indices of genetic contribution. However, these measures are better conceptualized as indices of risk that represent a combination of biopsychosocial influences (Zucker, Ellis, & Fitzgerald, 1994). Considerable research has focused on the association between family history and AUD, yet less attention has been paid to pain. This is surprising given that several mechanisms likely contribute to both conditions (e.g., Yeung, Craggs, & Gizer, 2017).

Genetics and epigenetics. Twin studies suggest 43% - 53% of the variability in AUD and 25% - 50% of the variability in chronic pain are due to genetic factors (Nielsen, Knudsen, & Steingrimsdottir, 2012; Verhulst, Neale, & Kendler, 2015). Considering the large heritability estimates and significant neurobiological overlap (Egli et al., 2012), it is believed that some genetic variants may confer risk for both AUD and chronic pain (Yeung et al., 2017). A recently published review of genetic association studies underscores the possibility of shared genetic liability, and polymorphisms within genes involved in dopamine (e.g., *ANKK1*) and opioid (e.g., *OPRM1*) neurotransmitter systems were identified as having the strongest overlap with respect to AUD and chronic pain (Yeung et al., 2017). Pre-clinical studies using rodents selectively bred for divergent alcohol preferences have also demonstrated evidence of covariation between alcohol preference and pain reactivity (e.g., Chester, Price, & Froehlich, 2002; Kampov-Polevoy et al., 1996).

Alcohol and pain trajectories may also be influenced by heritable changes in gene expression that do not involve changes to DNA sequence (i.e., epigenetics; Wolffe & Guschin, 2000). Exposure to environmental toxicants is one source of epigenetic effects (Bollati & Baccarelli, 2010). For example, alcohol consumption in fathers prior to conception is believed to cause changes in offspring via effects on the paternal germline (Cicero, 1994; Curley, Mashoodh,

& Champagne, 2011). Substantial evidence in support of this notion comes from animal studies in which genetics and the environment can be carefully controlled. For instance, Finegersh and Homanics (2014) exposed male mice to chronic alcohol or control conditions, mated them to alcohol-naïve females, and tested the adult offspring on several outcomes. Alcohol exposure was found to decrease DNA methylation at the *Bdnf* promoter of paternal germs cells and this hypo-methylation persisted in the brains of male and female offspring. Alcohol-sired male offspring also demonstrated enhanced sensitivity to the anxiolytic and motor-stimulating effects of alcohol and showed increased *Bdnf* expression in the ventral tegmental area relative to control-sired male offspring (Finegersh & Homanics, 2014). Similarly, adult alcohol-sired rats (vs. control-sired rats) have demonstrated hormonal abnormalities, including lower levels of beta-endorphin, an opioid peptide believed to be involved in the descending inhibition of pain (Bäckryd, Ghafouri, Larsson, & Gerdle, 2014; Cicero et al., 1990; Sprouse-Blum, Smith, Sugai, & Parsa, 2010). Taken together, these results suggest that pre-conceptual alcohol consumption in men has the potential to induce biochemical and behavioral changes in their offspring that may affect alcohol use and pain outcomes.

Psychosocial influence. It is important to recognize that family history of AUD imparts influence beyond genetic effects. The family, as a social context, is thought to be capable of promoting the development and maintenance of AUD and pain (e.g., Mares, van der Vorst, Engels, & Lichtwarck-Aschoff, 2011; Roy, 1982; Violon & Giurgea, 1984). Children raised by parents with AUD may be particularly vulnerable, as their homes likely share an atmosphere of tension, anxiety, and unpredictability (Woititz, 1983). Certain parent-child interpersonal patterns have also been shown to influence alcohol and pain outcomes. For example, parental modeling of drinking behavior has been associated with earlier initiation of alcohol use and increased

future consumption (Ryan, Jorm, & Lubman, 2010), and solicitous parental responding to child pain (e.g., continuously attending to pain symptoms) has been associated with greater functional disability in children with chronic abdominal pain (Walker & Zeman, 1992). Parental AUD has also been linked to physical and sexual child abuse (e.g., Miller, Maguin, & Downs, 1997; Vogeltanz et al., 1999), which in turn has been associated with the experience of chronic pain (e.g., Drossman et al., 1990; Walsh, Jamieson, MacMillan, & Boyle, 2007).

Family History as a Multifaceted Risk Factor

There is reason to believe that family history of AUD may serve as a risk factor for AUD *and* chronic pain. Consistent with a reciprocal model of substance use and pain (Ditre, Zale, & LaRowe, 2019; Zale, Maisto, & Ditre, 2015), both conditions may interact synergistically, engendering the escalation of drinking and pain among FH+ individuals. However, more research is needed to develop the current understanding of family history of AUD as it relates to pain perception. Although heightened pain sensitivity has been observed among individuals with a family history of AUD, we are not aware of any research to date that has examined clinically-relevant pain modulatory outcomes, such as CPM, OA, and TS, in this population.

The Current Study

The goal of the current study was to test whether endogenous pain modulatory processes (i.e., CPM, OA, and TS) differ as a function of family history of AUD among a sample of moderate-to-heavy drinkers who had not yet developed chronic pain. Analyses were conducted using data collected from a primary experimental study of bidirectional pain-alcohol effects (5R01AA024844). We hypothesized that a family history of AUD would be associated with a pro-nociceptive pain modulation profile. That is, participants with a family history of AUD (relative to those without) would demonstrate less efficient inhibition (i.e., CPM/OA) and/or

greater facilitation (i.e., TS) to experimentally induced pain. Given that the effects of family history of AUD may vary depending on the relationship to affected relatives (e.g., fathers vs. mothers; Chassin, Curran, Hussong, & Colder, 1996), an exploratory aim was to compare the effects of paternal and maternal histories of AUD.

Method

Participants

Participants were recruited from the local community through newspaper and internet advertisements for a primary study examining bidirectional pain-alcohol effects. Prospective participants were screened by telephone to assess study eligibility. Criteria for inclusion were: (1) 21 - 65 years of age; and (2) classified as a moderate or heavy drinker as assessed by the Quantity-Frequency Variability Index (QFV; Cahalan, Cisin, & Crossley, 1969). Exclusion criteria included: (1) current acute or chronic pain; (2) current use of prescription pain medications; (3) any possibility of being pregnant; (4) self-reported history of or treatment for psychiatric or alcohol/other drug problems; (5) medical conditions that contraindicate the use of alcohol; or (6) chili pepper allergies. A total of 235 participants completed the baseline assessment and pain modulatory measures (see Figure 1).

Measures and Materials

Family history of AUD. Participants were interviewed using an abridged version of the Family History Assessment Module (FHAM; Rice et al., 1995) that included items pertaining solely to alcohol use. The FHAM is a structured diagnostic interview used to assess DSM-III-R psychiatric disorders among relatives of the informant. Consistent with previous research (e.g., Curran et al., 1999), participants were queried about their biological parents, siblings, grandparents, and children. Three questions were used to screen relatives for alcohol problems

(e.g., "Has drinking ever caused any of your relatives to have problems with health, family, job, or police?"). For each positively screened relative, a corresponding Individual Assessment Module (IAM) was administered to assess DSM-III-R symptoms of alcohol abuse/dependence. The FHAM has demonstrated excellent specificity and moderate sensitivity for diagnosis of relatives' alcohol dependence (Rice et al., 1995).

The Feighner criteria for alcoholism was applied to each IAM, yielding either "definite diagnosis", "probable diagnosis", "unknown," or "negative" codes (Feighner et al., 1972). Consistent with previous research (e.g., Curran et al., 1999; Stoltenberg et al., 1998), definite and probable diagnoses were collapsed. Family history positive (FH+) participants were defined as those with one or both parents with a history of AUD, whereas family history negative (FH-) participants were defined as those without a history of AUD in either parent. Emphasis was placed on parents for several reasons. Dichotomous measures that partition on the basis of parental AUD are among the most frequently employed in family history research (e.g., Heitzeg, Nigg, Yau, Zucker, & Zubieta, 2010; Nirenberg, Liepman, Begin, Maisto, & Liebermann, 1990; Vaidya et al., 2019). Parents are also uniquely positioned to influence pain outcomes in their offspring via genetic, epigenetic, and psychosocial effects (e.g., Denk & McMahon, 2012; Mogil, 2012; Palermo & Eccleston, 2009). For exploratory analyses, participants with histories of paternal (PH+) and maternal (MH+) AUD were examined separately. Participants without a history of AUD in either parent were deemed paternal/maternal history negative (i.e., FH-).

Quantitative sensory testing apparatus. The Medoc Q-Sense CPM System (Medoc Ltd., Ramat Yishai, Israel) was used to deliver contact-heat pain via 30 x 30 mm Peltier-based thermodes. The thermodes have a temperature range of 16°C - 50°C. Depending on the particular test, pain ratings are made either with a remote push-button response device or a computerized

visual analog scale (CoVAS). CoVAS anchor points ranging from 0 (*no pain*) to 100 (*most intense pain imaginable*) were provided. Details specific to each test are described below.

Psychophysical parameters. Prior to assessment of endogenous pain modulatory processes, pain threshold and pain tolerance were assessed using a test of limits protocol (Geva, Pruessner, & Defrin, 2014). Six trials of stimuli were administered to the non-dominant forearm at 30-second intervals, with each stimulus increasing in temperature from 32°C at a rate of 1°C per second. For the first three trials, participants indicated when they first perceived the stimulus as painful (threshold) using the remote push-button response device. During the last three trials, participants indicated when they were no longer willing to tolerate the stimulus (tolerance) using the same response device. Following each response, the temperature was recorded and began to return to 32°C at a rate of 1°C per second. Temperatures recorded during the first and last three trials were averaged to generate mean threshold and tolerance values, respectively. These data were then used to compute the supra-threshold (i.e., the midpoint temperature between threshold and tolerance). Individual supra-thresholds were later used as destination temperatures in endogenous pain modulatory assessments.

Conditioned pain modulation. We utilized a single test-stimulus protocol that has previously demonstrated favorable test-retest reliability (Granovsky, Miller-Barmak, Goldstein, Sprecher, & Yarnitsky, 2016). The test-stimulus thermode was applied to the volar surface of the non-dominant forearm and the conditioning-stimulus thermode was applied to the dominant upper arm. Individual supra-thresholds were used as destination temperatures for both the test- and conditioning-stimuli. Prior to CPM assessment, participants were instructed to make continuous pain ratings of the test-stimulus only using the CoVAS. The test-stimulus increases in temperature from 32°C at a rate of 2°C per second until supra-threshold is reached, where it

plateaus for 45 seconds. Exactly 20 seconds into this sequence, the conditioning-stimulus increases in temperature from 32°C at a rate of 2°C per second until supra-threshold is reached, where it plateaus for 25 seconds. Both stimuli then return to 32°C at a rate of 1°C per second. The final CPM effect is then computed as the difference between mean pain ratings during the 10-second epoch after the conditioning-stimulus reaches supra-threshold and the 10-second epoch preceding initiation of the conditioning-stimulus (i.e., CPM = $\text{CoVAS}_{\text{Test-Stimulus + Conditioning-Stimulus}}$ - $\text{CoVAS}_{\text{Test-Stimulus}}$). Thus, evidence of pain inhibition is denoted by negative values.

Offset analgesia. OA protocols typically involve pain ratings during a contiguous three-temperature stimulus sequence (e.g., 49°C, 50°C, 49°C), where the OA effect is characterized by a disproportionately large reduction in pain after an incremental decrease in the temperature of the stimulus (Grill & Coghill, 2002). We employed the same approach, using individual supra-thresholds as the maximum temperature reached during a three-temperature stimulus sequence. The stimulus thermode was applied to the volar surface of the non-dominant forearm. Prior to OA assessment, participants were instructed to make continuous pain ratings of the stimulus using the CoVAS. During the first sequence, the stimulus increases in temperature from 32°C at a rate of 2°C per second until reaching 1°C below supra-threshold, where it plateaus for 5 seconds (T1). The stimulus then increases in temperature at a rate of 1°C per second until supra-threshold is reached, where it plateaus for 5 seconds (T2). The stimulus then decreases in temperature at a rate of 1°C per second until reaching 1°C below supra-threshold, where it plateaus for 20 seconds (T3). The stimulus then returns to 32°C at a rate of 1°C per second. The final OA effect is then computed as the difference between the maximum pain rating during the T2 epoch and the minimum pain rating during the T3 epoch (i.e., OA = $\text{CoVAS}_{\text{MaxT2}}$ - $\text{CoVAS}_{\text{MinT3}}$). Thus, evidence of pain inhibition is denoted by positive values.

Temporal summation. TS protocols utilize repetitive-phasic or tonic pain stimuli. Here, we used a tonic heat stimulus protocol, which, relative to repetitive-phasic heat stimulus protocols, is believed to evoke a shared mechanism of central pain modulation (Granot et al., 2006). The stimulus thermode was applied to the volar surface of the non-dominant forearm. Prior to TS assessment, participants were instructed to make continuous pain ratings of the stimulus using the CoVAS. The stimulus increases in temperature from 32°C at a rate of 1°C per second until supra-threshold is reached, where it plateaus for 1 minute. The stimulus then returns to 32°C at a rate of 1°C per second. The final TS effect is then computed as the difference between the last pain rating during the 1-minute epoch and the first pain rating during the 1-minute epoch (i.e., TS = $CoVAS_{Last}$ - $CoVAS_{First}$). Thus, evidence of pain facilitation is denoted by positive values.

Alcohol consumption pattern. The Quantity-Frequency Variability Index (QFV; Cahalan et al., 1969) was used to assess patterns of alcohol consumption. Participants reported, over the previous three months, the types of alcoholic beverages they drank, their frequency of consumption, and how much they usually drank during these occasions. Per inclusion criteria, alcohol consumption patterns in the current sample were classified as moderate or heavy. The QFV has shown good reliability and validity (Cahalan et al., 1969).

Sociodemographic characteristics. Participants reported a range of sociodemographic characteristics, including age, race, ethnicity, biological sex, education, marital status, and annual income.

Procedure

After telephone screening, eligible participants were scheduled for two study visits, no more than one week apart, and asked to refrain from using alcohol or other illicit substances for

at least 24 hours prior to their appointments. Participants provided informed consent and

completed measures to verify eligibility at the first visit. During the first visit, eligible

participants also completed self-report questionnaires and a structured interview to assess family

history of AUD. Given that procedures were counterbalanced across sessions in the parent study,

participants completed the QST assessment during either their first or second appointment. Pain

modulatory assessments were conducted in in the following order: (1) CPM; (2) OA; (3) TS.

Participants were compensated up to $106 for completing the first visit and up to $132 for

completing the second visit. Procedural details are shown in Figure 2.

Power Analysis

An *a priori* power analysis was performed using the program G*Power (Faul, Erdfelder,

Lang, & Buchner, 2007) to estimate the sample size necessary for the current study. This

analysis was based on data from Stewart et al. (1995), comparing pain sensitivity between FH+

and FH- participants (N = 81). Considering the dearth of research investigating family history of

AUD in relation to pain outcomes, this reference was selected for effect size estimation. Using

Cohen's (1988) criteria, the effect size in this study was medium ($f = .31$). Thus, with an alpha

value of 0.05 and power level of 0.80, the required sample size was approximately 70 ($n = 35$ per

group).

Data Analytic Plan

Analyses were conducted using SPSS Statistics 27 (IBM SPSS Statistics, 2012). First,

continuous variables were compared with a *t*-test and categorical variables with the chi-square

test for independent groups (i.e., FH+ vs. FH-). Mean and standard deviations were computed for

continuous variables, whereas frequencies and percentages were computed for categorical

variables. An alpha value of 0.05 was used as the criterion for statistical significance. Preliminary analyses were also conducted to ensure no violation of parametric assumptions.

For the primary aim, we tested the effects of family history of AUD (i.e., FH+ vs. FH-) on CPM, OA, and TS using Multivariate Analysis of Covariance (MANCOVA). Multivariate analysis, as opposed to separate univariate analyses, was selected as CPM, OA, and TS tend to be correlated (e.g., Honigman, Yarnitsky, Sprecher, & Weissman-Fogel, 2013; Nahman-Averbuch et al., 2011) and are conceptually linked in that they all reflect endogenous pain modulatory processes. When outcomes are correlated, MANCOVA affords greater statistical power and has the advantage of limiting the family-wise error rate relative to separate univariate analyses (Bray & Maxwell, 1985; Tabachnick, Fidell, & Ullman, 2007). Covariates selected *a priori* included age and biological sex, given previously documented associations with CPM (e.g., Hermans, Van Oosterwijck, et al., 2016), OA (e.g., Nahman-Averbuch et al., 2016; Naugle, Cruz-Almeida, Fillingim, & Riley, 2013), and TS (e.g., Edwards & Fillingim, 2001; Robinson, Wise, Gagnon, Fillingim, & Price, 2004). Because we were interested in testing the effects of family history of AUD above and beyond that of alcohol consumption pattern, QFV category was also included as a covariate. For the exploratory aim, the analysis above was repeated comparing individuals who endorsed histories of paternal vs. maternal AUD separately to more specifically examine parental contribution. To conserve cell sizes, participants with histories of AUD in both parents were deemed PH+ and MH+.

Outliers can have detrimental effects on statistical analyses by increasing error variance and reducing power, decreasing normality, and increasing the odds of making Type I and Type II errors (e.g., Osborne & Overbay, 2004). Psychophysiological measures are especially prone to outliers, largely due to their indirect nature (Cacioppo, Tassinary, & Berntson, 2007). For

example, QST measures events occurring outside the participant's body (i.e., movements of the CoVAS) that are reflective of internal events (i.e., pain perception). Thus, the signal is subject to some distortion, periodically creating artifacts that should be removed prior to statistical analysis (Cacioppo et al., 2007). For these reasons, we detected and excluded cases ± 3 median absolute deviations from each outcome. This is a conservative method for handling outliers that has been recommended by researchers and statisticians (e.g., Kannan, Manoj, & Arumugam, 2015; Leys, Ley, Klein, Bernard, & Licata, 2013). Twenty-three outliers were excluded from the primary analysis (FH+: $n = 8$; FH-: $n = 15$). For the exploratory aim, 19 outliers were excluded from the paternal analysis (PH+: $n = 4$; FH-: $n = 15$) and 20 outliers were excluded from the maternal analysis (MH+: $n = 5$; FH-: $n = 15$). Sensitivity analyses were performed to examine whether results differed as a consequence of outlier exclusion.

Results

Participant Characteristics

Participants included 235 moderate-to-heavy drinkers (66% heavy; $M_{age} = 34.3$, $SD = 12.3$). The sample was predominantly male (58.3%), non-Hispanic (91.9%), white (60%), and single (72.3%). Approximately 40% of participants reported a household income of less than $20,000 per year and having a high school degree or less in terms of education. Structured diagnostic interviews (FHAM) revealed that 23% of the sample was FH+ ($n = 54$). Among the FH+ participants, 9 reported history of AUD in both father and mother, 29 reported only paternal history of AUD, and 16 reported only maternal history of AUD. No differences were observed between FH+ and FH- groups with regard to any sociodemographic variables. Additional sociodemographic, family history, and drinking pattern data are presented in Table 1.

Parametric Assumption Testing

Preliminary testing of parametric assumptions revealed that the data was normally distributed, as assessed by inspection of Q-Q plots and skewness and kurtosis; there were no multivariate outliers, as assessed by Mahalanobis distance ($p > .001$); there were linear relationships between outcome variables for each group, as assessed by scatterplot; there was no multicollinearity ($|r| < .9$); and there was homogeneity of variance-covariance matrices, as assessed by Box's M test ($p = .014$). There was also evidence of a linear relationship between the covariate age and each of the outcome variables for FH+ and FH- participants, as assessed by inspection of scatterplots. Additionally, there was homogeneity of regression slopes, as assessed by the interaction term between age and family history group (F [3, 204] = .744, $p = .527$).

Family History of AUD and Endogenous Pain Modulatory Function

Consistent with expectation, MANCOVA indicated a statistically significant difference between FH+ and FH- participants on the combined dependent variable (F [3, 205] = 2.785, $p = .042$; Wilks' $\Lambda = .961$; partial $\eta^2 = .039$), accounting for nearly 4% of the variance in endogenous pain modulatory function. The effect of the covariate age was also significant (F [3, 205] = 3.441, $p = .018$; Wilks' $\Lambda = .952$; partial $\eta^2 = .048$), whereas biological sex and QFV category were not (ps > .05). Univariate follow-up tests revealed a significant difference in OA scores between FH+ and FH- participants (F [1, 207] = 7.747, $p = .006$, partial $\eta^2 = .036$), with adjusted means of 21.00 (95% $CI = 12.92, 29.07$) and 33.70 (95% $CI = 29.32, 38.08$), respectively (Figure 3). No differences were observed for CPM (F [1, 207] = 2.320, $p = .129$, partial $\eta^2 = .011$) or TS scores (F [1, 207] < 0.001, $p = .992$, partial $\eta^2 < .001$). The adjusted means for all dependent variables are presented in Table 2.

Paternal vs. Maternal Histories of AUD

Exploratory MANCOVA indicated a significant difference between PH+ and FH-participants on the combined dependent variable (F [3, 193] = 2.760, p = .043; Wilks' Λ = .959; partial η^2 = .041). Again, the covariate age was significant (F [3, 193] = 3.921, p = .010; Wilks' Λ = .943; partial η^2 = .057), whereas biological sex and QFV category were not (ps > .05). Univariate follow-up tests revealed significant differences in CPM (F [1, 195] = 5.287, p = .023, partial η^2 = .026) and OA scores (F [1, 195] = 5.470, p = .020, partial η^2 = .027) between PH+ and FH- participants, but not TS scores (F [1, 195] = 0.161, p = .688, partial η^2 = .001). Participants in the PH+ group demonstrated higher (i.e., less efficient) CPM scores and lower OA scores relative to FH- participants, with adjusted mean differences of 6.09 (95% CI = 0.87, 11.31) and -12.43 (95% CI = -22.91, -1.95), respectively (Figures 4 and 5). In contrast to the paternal MANCOVA, no differences were observed between MH+ and FH- participants on the combined dependent variable (F [3, 179] = .884, p = .451; Wilks' Λ = .985; partial η^2 = .015). The adjusted means for exploratory subgroup analyses are presented in Tables 3 and 4.

Sensitivity Analyses

Sensitivity analyses revealed that the primary analysis comparing FH+ vs. FH-participants on the combined dependent variable was no longer statistically significant when outliers were included (F [3, 228] = .970, p = .073; Wilks' Λ = .970; partial η^2 = .030). Inclusion of outliers did not influence the pattern of results for the paternal (i.e., PH+ vs. FH-; F [3, 212] = .946, p = .008; Wilks' Λ = .946; partial η^2 = .054) and maternal (i.e., MH+ vs. FH-; F [3, 199] = .249, p = .862; Wilks' Λ = .996; partial η^2 = .004) exploratory analyses. Significant univariate differences between PH+ and FH- participants were still detected for CPM and OA (ps < .05). Participants in the PH+ group demonstrated higher (i.e., less efficient) CPM scores and lower

OA scores relative to FH- participants, with adjusted mean differences of 10.21 (95% *CI* = 3.20, 17.22) and -11.82 (95% *CI* = -22.02, -1.63), respectively.

Discussion

The current study represents the first demonstration of altered pain modulatory function among individuals with a family history of AUD. As hypothesized, moderate-to-heavy drinkers with a family history of AUD (relative to those without) evinced a pro-nociceptive pain modulation profile in response to experimental pain testing. Specifically, family history of AUD was associated with deficits in pain-inhibitory processes, such as OA and CPM. Here, low-efficiency pain inhibition places participants on the pro-nociceptive end of the clinical spectrum between pro- and anti-nociception (Yarnitsky et al., 2014). Group differences were also observed after controlling for the variance attributable to QFV category, suggesting the effects of family history were independent of alcohol consumption pattern. Further, the exploratory analyses suggest these effects may be driven by paternal history of AUD.

Collectively, these findings contribute to a nascent literature implicating family history of AUD in pain perception and potential for developing chronic pain. Stewart and colleagues (1995) documented heightened pain sensitivity among FH+ participants using aversive electrical stimulation and static pain intensity rating scales. The current study expands upon this finding by providing evidence that family history of AUD may also influence dynamic and clinically-relevant pain modulatory processes. These results might help to clarify the high rates of familial AUD observed among chronic pain patients (Goldberg et al., 1999; Katon et al., 1985; Pecukonis, 2004). Indeed, previous studies have underscored the pathophysiological role of dysfunctional pain modulation in the development of chronic pain (e.g., Wilder-Smith et al.,

2010; Yarnitsky et al., 2008). Family history of AUD may therefore confer risk for chronic pain via its effects on endogenous pain-inhibitory systems.

The current study design prevents mechanistic conclusions from being drawn regarding the associations between family history of AUD and pain modulatory outcomes. However, some insight may be gleaned from prior research. For example, certain genetic polymorphisms (e.g., within the serotonin-transporter-linked polymorphic region in *SLC6A4*) have been implicated in both AUD (e.g., Feinn, Nellissery, & Kranzler, 2005) and endogenous pain modulation (e.g., Lindstedt et al., 2011). To our knowledge, these relations have not been tested under one overarching paradigm, but they do emphasize the possibility of common genetic liability. It is also worth noting that OA was the dynamic test paradigm most strongly associated with family history of AUD. This is perhaps unsurprising given that OA likely evaluates more brain derived pain modulation than CPM and TS (Hermans, Calders, et al., 2016; Price & Dubner, 1977), and a substantial literature indicates differences in brain structure and function between FH+ and FH-individuals (e.g., Cservenka, 2016). Additionally, exploratory analyses intended to examine potential differences in parental contribution emphasized the role of fathers. In drawing from the extant animal literature, one could invoke epigenetic effects of pre-conceptual alcohol exposure in males. For instance, adult alcohol-sired rats have exhibited lower levels of beta-endorphin in the hypothalamus relative to control-sired rats (i.e., those whose fathers were not chronically exposed to alcohol prior to mating; Cicero et al., 1990). The neurobiology subserving the descending modulation of pain originates in the hypothalamus, among other key brain regions (Ossipov et al., 2010; Puopolo, 2019). In response to pain, hypothalamic release of beta-endorphin in the periaqueductal gray region inhibits the release of GABA, facilitating descending pain-inhibitory projections to the spinal cord (Ossipov et al., 2010; Sprouse-Blum et

al., 2010). In the context of the current study, paternal history of AUD may have been associated with reduced endogenous pain inhibition, in part, due to lower beta-endorphin levels. Supporting this notion, prior clinical research has found that patients with chronic neuropathic pain have lower levels of beta-endorphin in their cerebrospinal fluid compared to healthy controls (Bäckryd et al., 2014).

Strengths of the current study include the relatively large sample size, recruitment of drinkers from the general population, and use of established QST pain assessment methods. However, several limitations should be noted. First, the sample was comprised of moderate-to-heavy drinkers with no indication of AUD. Future research would benefit from testing these relations among infrequent-to-light drinkers, abstainers, and those with AUD. Despite statistically controlling for QFV category in our models, alcohol consumption patterns were restricted to those classified as moderate or heavy. It is therefore unclear whether the effects of family history of AUD would be consistent across individuals with varied drinking patterns. Second, our power analysis estimated a required sample size of 70 ($n = 35$ per group). Thus, the exploratory subgroup analysis comparing MH+ vs. FH- participants was likely underpowered (MH+: $n = 20$; FH-: $n = 166$), increasing the likelihood of a false negative finding (Burke, Sussman, Kent, & Hayward, 2015). Third, although family history interviews have been found to be a valid source of diagnostic information, sensitivity may be diminished when relying on a single informant (Andreasen, Rice, Endicott, Reich, & Coryell, 1986; Rice et al., 1995). Fourth, additional research will be needed to determine whether differential pain modulatory function in individuals with a family history of AUD predicts the development of chronic pain. Finally, future laboratory-based pain studies drawing from a more diverse sample would supplement the

current findings and help clarify the conflicting literature on racial/ethnic differences in experimental pain reactivity (Peacock & Patel, 2008).

The current analyses provide evidence that family history of AUD may influence clinically-relevant pain modulatory outcomes. A deeper understanding of this relationship may eventually promote early identification and treatment of individuals at risk for chronic pain. Indeed, family history assessment is believed to be the most cost-effective means of screening individuals at risk for certain disorders, especially for those with a strong genetic basis (Bennett, 2010). Increased awareness of the connection between family history of AUD and pain may also inform treatment decisions for acute pain among FH+ individuals. For example, healthcare providers might elect to use more comprehensive and interdisciplinary pain management approaches (e.g., multimodal analgesia, cognitive-behavioral therapy, etc.) in efforts to prevent the development of chronic pain among those with a family history of AUD (McGreevy, Bottros, & Raja, 2011).

In conclusion, results of the current study indicate altered pain modulatory function among individuals with a family history of AUD. These findings suggest that individuals with a family history of AUD may represent a population that is particularly vulnerable to the development of chronic pain.

Table 1

Sociodemographic, Family History, and Drinking Pattern Characteristics

	Total Sample	Family History of AUD		QFV Category	
		FH-	FH+	Moderate	Heavy
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Gender					
Male	137 (58.3%)	108 (59.7%)	29 (53.7%)	41 (51.3%)	96 (61.9%)
Female	98 (41.7%)	73 (40.3%)	25 (46.3%)	39 (48.8%)	59 (38.1%)
Ethnicity					
Non-Hispanic	216 (91.9%)	168 (92.8%)	48 (88.9%)	72 (90.0%)	144 (92.9%)
Race					
White	141 (60.0%)	109 (60.2%)	32 (59.3%)	54 (67.5%)	87 (56.1%)
Black	86 (36.6%)	68 (37.6%)	18 (33.3%)	23 (28.8%)	63 (40.6%)
Other	8 (3.4%)	4 (2.2%)	4 (7.4%)	3 (3.8%)	5 (3.2%)
Marital Status					
Single	170 (72.3%)	130 (71.8%)	40 (74.1%)	53 (66.3%)	117 (75.5%)
Married	31 (13.2%)	25 (13.8%)	6 (11.1%)	14 (17.5%)	17 (11.0%)
Separated/Divorced/Widowed	34 (14.5%)	26 (14.4%)	8 (14.8%)	13 (16.3%)	21 (13.5%)
Education					
Did Not Graduate High School	12 (5.1%)	12 (6.6%)	0 (0.0%)	0 (0.0%)**	12 (7.7%)**
High School Graduate	78 (33.2%)	57 (31.5%)	21 (38.9%)	16 (20.0%)**	62 (40.0%)**
Some College or Greater	145 (61.7%)	112 (61.9%)	33 (61.1%)	64 (80.0%)**	81 (52.3%)**
Annual Household Income					
Less Than $10,000	60 (25.5%)	50 (27.6%)	10 (18.5%)	11 (13.8%)*	49 (31.6%)*
$10,000 - $19,999	41 (17.4%)	28 (15.5%)	13 (24.1%)	13 (16.3%)*	28 (18.1%)*
$20,000 - $29,999	43 (18.3%)	33 (18.2%)	10 (18.5%)	20 (25.0%)*	23 (14.8%)*
$30,000 - $39,999	24 (10.2%)	19 (10.5%)	5 (9.3%)	11 (13.8%)*	13 (8.4%)*
Greater Than $40,000	67 (28.5%)	51 (28.2%)	16 (29.6%)	25 (31.3%)*	42 (27.1%)*
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Age	34.34 (12.30)	34.32 (12.51)	34.41 (11.70)	32.84 (11.79)	35.12 (12.52)

Note. FH- = family history negative (those without a history of AUD in either parent); FH+ = family history positive (those having one or both parents with a history of AUD); QFV = Quantity-Frequency Variability Index; * $p < .05$; ** $p < .01$.

Table 2

Adjusted Means of Pain Modulatory Outcomes as a Function of Family History of AUD

	FH-	FH+	
	M (SE)	M (SE)	F (1, 207)
Conditioned Pain Modulation	-4.41 (1.12)	-0.91 (2.06)	2.32
Offset Analgesia	33.70 (2.22)	21.00 (4.10)	7.75**
Temporal Summation	8.35 (2.08)	8.40 (3.83)	<0.01

Note. AUD = alcohol use disorder; FH- = family history negative (those without a history of AUD in either parent); FH+ = family history positive (those with one or both parents with a history of AUD); * $p < .05$; ** $p < .01$.

Table 3

Adjusted Means of Pain Modulatory Outcomes as a Function of Paternal History of AUD

	FH-	PH+	
	M (SE)	M (SE)	F (1, 195)
Conditioned Pain Modulation	-4.35 (1.14)	1.74 (2.47)	5.29*
Offset Analgesia	33.70 (2.28)	21.27 (4.95)	5.47*
Temporal Summation	8.53 (2.15)	10.53 (4.66)	0.16

Note. AUD = alcohol use disorder; FH- = family history negative (those without a history of AUD in either parent); PH+ = paternal history positive (those with a father with a history of AUD); * $p < .05$; ** $p < .01$.

Table 4

Adjusted Means of Pain Modulatory Outcomes as a Function of Maternal History of AUD

	FH-	MH+	
	M (SE)	M (SE)	F (1, 181)
Conditioned Pain Modulation	-4.20 (1.11)	-5.44 (3.03)	0.15
Offset Analgesia	33.31 (2.30)	23.97 (6.29)	1.92
Temporal Summation	8.49 (2.16)	9.95 (5.92)	0.05

Note. AUD = alcohol use disorder; FH- = family history negative (those without a history of AUD in either parent); MH+ = maternal history positive (those with a mother with a history of AUD); * $p < .05$; ** $p < .01$.
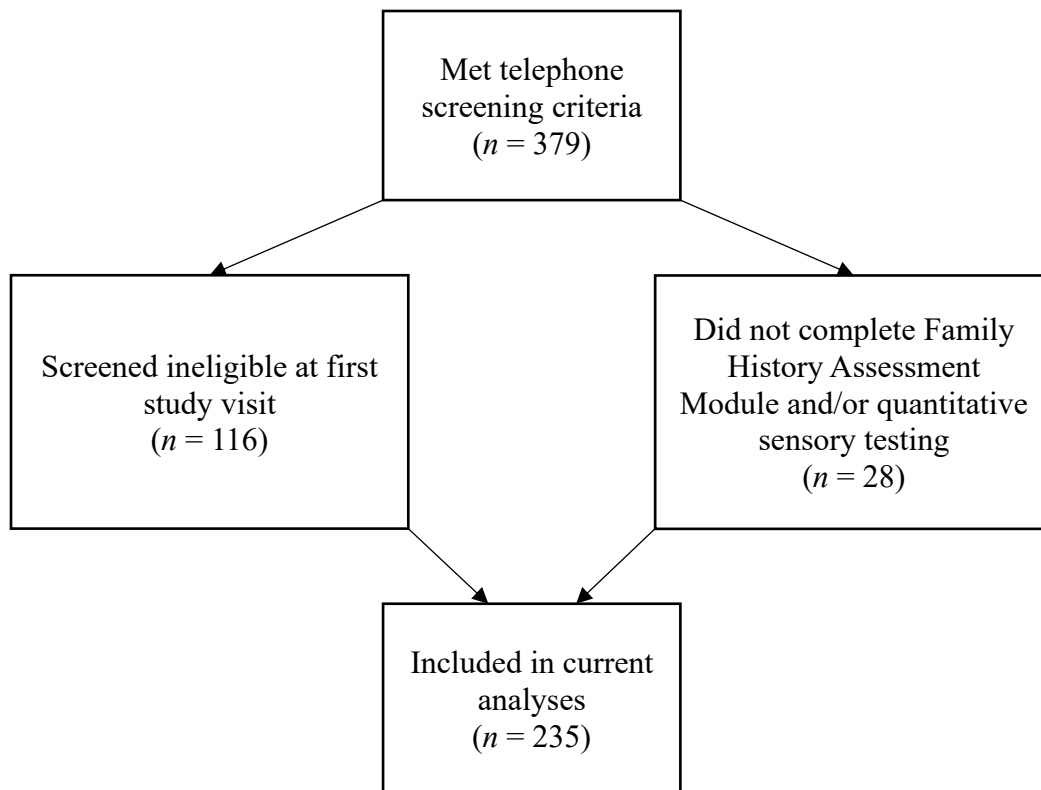
Figure 1. Inclusion of Participants.

| Recruitment	Telephone Screening	Eligible Participants:	Baseline	Quantitative Sensory Testing
Responded to an ad for a research study about alcohol, mood, and sensory function	Screened for inclusion and exclusion criteria	Scheduled and asked to refrain from using alcohol/other illicit substances for at least 24 hours prior to study visit	Informed consent; verification of study eligibility; self-report questionnaires, Family History Assessment Module	Conditioned pain modulation; offset analgesia; temporal summation

Figure 2. Study Procedure.
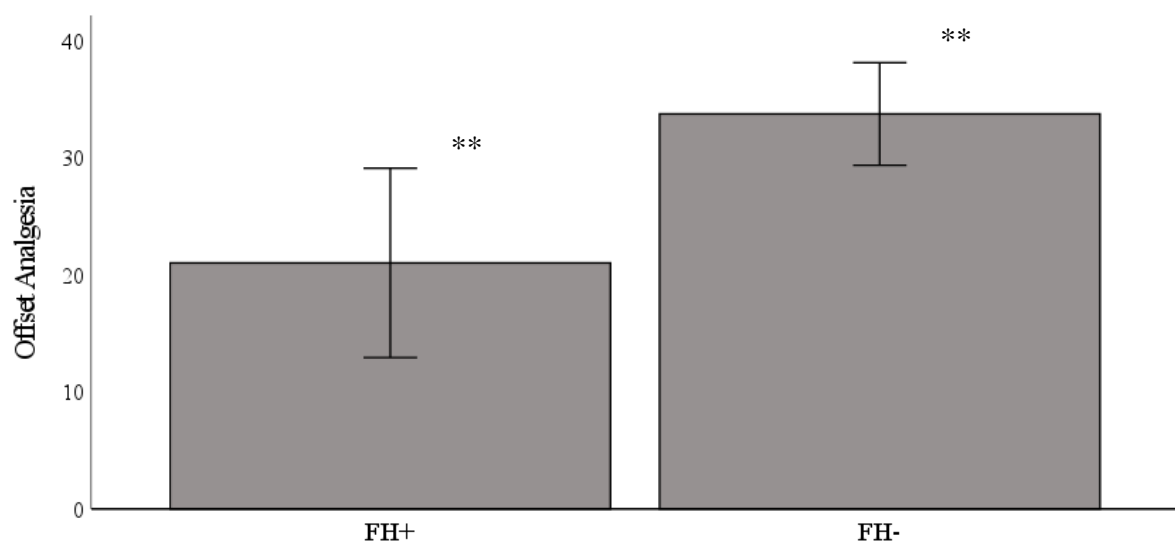
Figure 3. Offset Analgesia Scores as a Function of Family History of AUD.
Note. AUD = alcohol use disorder; FH+ = family history positive (those with one or both parents with a history of AUD); FH- = family history negative (those without a history of AUD in either parent); means statistically adjusted for age, biological sex, and drinking pattern (QFV category); error bars represent 95% *CI*; ** $p < .01$.
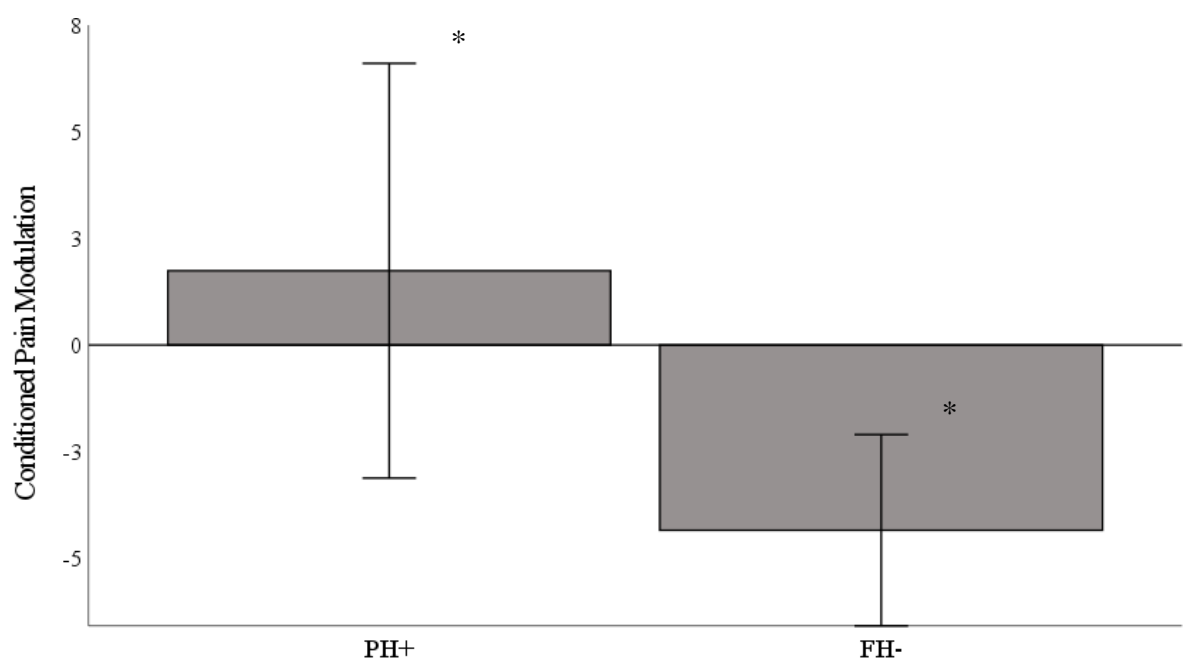
Figure 4. Conditioned Pain Modulation Scores as a Function of Paternal History of AUD.
Note. AUD = alcohol use disorder; PH+ = paternal history positive (those with a father with a history of AUD); FH- = family history negative (those without a history of AUD in either parent); means statistically adjusted for age, biological sex, and drinking pattern (QFV category); error bars represent 95% *CI*; * *p* < .05.

Figure 5. Offset Analgesia Scores as a Function of Paternal History of AUD.
Note. AUD = alcohol use disorder; PH+ = paternal history positive (those with a father with a history of AUD); FH- = family history negative (those without a history of AUD in either parent); means statistically adjusted for age, biological sex, and drinking pattern (QFV category); error bars represent 95% *CI*; * *p* < .05.
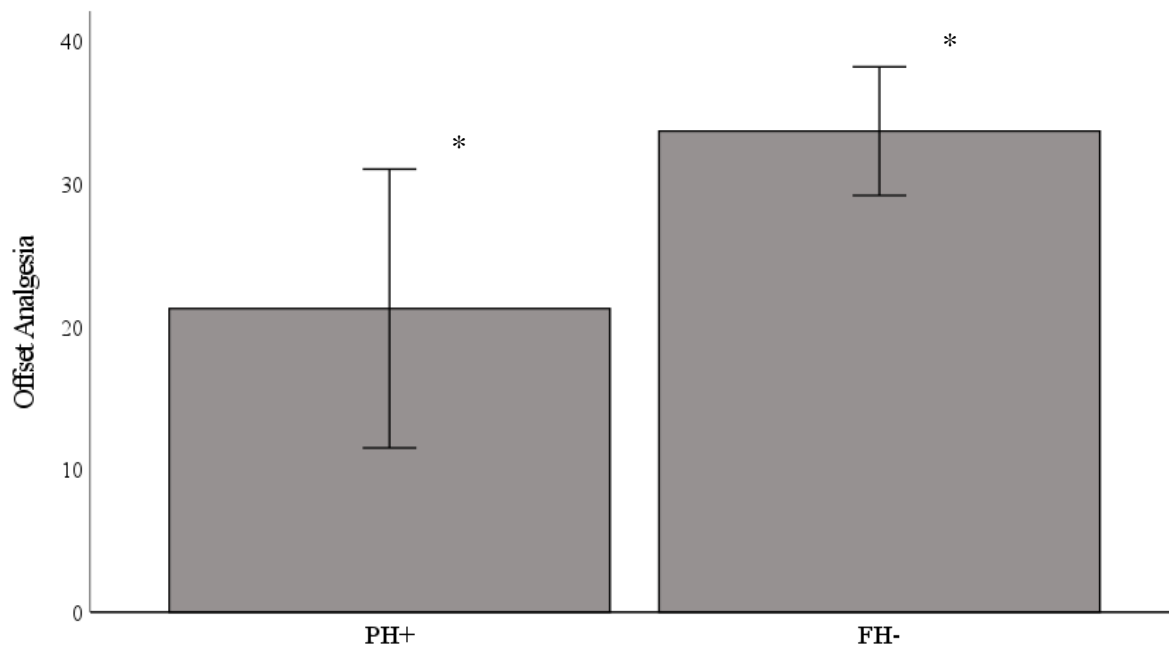
Appendix A

Family History Assessment Module (FHAM) - Screener

I would like to ask you some questions about your children, parents, sisters/brothers, and grandparents that you just mentioned in the family tree.

FOR EACH RELATIVE MENTIONED, RECORD NAME AND RELATIONSHIP.

1. Has drinking ever caused any of your relatives to have problems with health, family, job, or police?

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

2. Have any of your relatives ever talked to a doctor or a counselor about any problems with alcohol?

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

3. Have any of your relatives ever been hospitalized because of alcohol problems?

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

REL: _____

IF ANY RELATIVE MENTIONED IN Q. 2-3 <u>ONLY</u>, GO BACK AND RE-ASK APPROPRIATE SCREENING QUESTION (Q. 1). OTHERS CONTINUE.

4. So, none of the following relatives, that is… (**LIST RELATIVES NOT RECORDED IN Q. 1, 2, 3**), had any problems with alcohol?

ADMINISTER AN INDIVIDUAL ASSESSMENT MODULE (IAM) FOR EACH RELATIVE RECORDED IN THE FHAM SCREENER.

Appendix B

FHAM - Individual Assessment Module (IAM)

RELATIVE: _____

Would you say that you know/knew him/her well?

No   Yes   Unsure

When was the last time you had any contact with him/her?

Month/Year _____

Is this relative living?

No   Yes   Unsure

Because of drinking, did your (RELATIVE) ever have problems, such as:

	N	**Y**	**U**
1. using alcohol in larger amounts or over a longer period than s/he intended?	1	5	9
2. being unable to stop or cut down on drinking?	1	5	9
3. spending a lot of time drinking or being hung over?	1	5	9
4. being unable to work, go to school or take care of household responsibilities?	1	5	9
5. being high from drinking when s/he could get hurt?	1	5	9
6. having accidental injuries?	1	5	9
7. reducing or giving up important activities?	1	5	9
8. objections from family or friends, or at work or school?	1	5	9
9. having a legal problem (DWIs, arrests)?	1	5	9
10. having blackouts?	1	5	9
11. going on binges or benders, drinking 2 or more days without sobering up?	1	5	9
12. physical health problems (liver disease, pancreatitis)?	1	5	9
13. emotional or psychological problems (uninterested, depressed, suspicious/paranoid, having strange ideas)?	1	5	9
14. withdrawal symptoms (shakes, seizures/convulsions, DTs)?	1	5	9
15. needing to drink a great deal more in order to get an effect, or finding that s/he could no longer get drunk on the amount s/he used to drink?	1	5	9
16. any kind of treatment of hospitalization?	1	5	9
17. making rules to control drinking (never drinking alone, never drinking before 5 p.m.), drinking before breakfast, or drinking non-beverage alcohol like vanilla extract, cough syrup, or rubbing alcohol?	1	5	9
18. trouble at work or school or getting into fights while drinking?	1	5	9
19. losing friends because of his/her drinking, considering him/herself an excessive drinker, or feeling guilty about his/her drinking?	1	5	9

IF 3 OR MORE 5's CODED IN Q. 1-19, CONTINUE. OTHERS CONCLUDE.

20. Did (RELATIVE) have a period of a month or more when 3 or more of these experiences occurred together?

NO (SKIP TO 21)	1
YES	5
UNSURE (SKIP TO 21)	9

a. How old was (RELATIVE) the first/last time (he/she) had three or more of these experiences occurring within a period lasting a month or longer?

AGE ONSET:

AGE RECOVERED:

21. **OMIT PHRASE IN BRACKETS IF Q. 20 CODED NO.**
    [Since (RELATIVE) developed problems at about age (AGE ONSET ABOVE),] was there ever a period of three months or longer when (RELATIVE) did not have anything to drink?

NO (CONCLUDE)	1
YES	5
UNSURE (CONCLUDE)	9

a. How old was (RELATIVE) when these periods occurred?

AGE to AGE

Period 1 ___ to ___
Period 2 ___ to ___
Period 3 ___ to ___
Period 4 ___ to ___
Period 5 ___ to ___

Appendix C

FHAM - Diagnostic Scores

ALCOHOLISM (FEIGHNER):

Definite diagnosis: one or more items coded 5 in at least three of the following four groups:

I:	10, 11, 12, 14
II:	2, 17
III:	9, 18
IV:	8, 19

Probable diagnosis: two items coded 5 in two different groups, from the groups listed above
Unknown: combination of 5s and 9s are not enough to meet above two thresholds
Negative: total of 5s and 9s not enough to meet any of the above, or all above items coded 1

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