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Age of Alcohol Initiation and Reward Processes in a Current Alcohol Drinking Sample

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by

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Abstract

Earlier ages of alcohol initiation have been associated with an increased vulnerability for Alcohol Use Disorder and general risk taking behaviors beyond genetic influence. Reward processes, including reward anticipation (pleasure before receiving alcohol/general reward), reward learning (how quickly one pairs a stimulus with alcohol/general reward), and reward consummation (pleasure when receiving alcohol/general reward), have been implicated as potential mechanisms accounting for this vulnerability. However, no careful bio-behavioral research has been conducted on the effect of age of alcohol initiation on general and alcohol-related reward processes. Using Event Related Potentials (ERPs), the current study addressed this gap in a sample of 123 current alcohol drinkers. The Monetary Incentive Delay-General task and Monetary Incentive Delay-Alcohol task were administered to participants, in which reward learning (quickness of pairing the neutral cue or alcohol cue with monetary feedback), reward anticipation (activity to neutral cue or alcohol cue), and reward consummation (activity to monetary feedback) were examined. Electroencephalography was used to collect ERPs that index reward anticipation (P3) and reward consummation (P3 and Late Positive Potential) during these tasks. Earlier ages of alcohol initiation were associated with increased alcohol-related reward learning and decreased alcohol-related reward consummation (P3 and Late Positive Potential) beyond genetic and environmental covariates. There were no other significant relationships. These findings support and extend alcohol theories by showing that earlier ages of alcohol initiation may foster a greater sensitization in alcohol-specific reward-learning and more pronounced decreases in alcohol-related consummation. Although in need of direct testing, this might explain why earlier ages of alcohol initiation are associated with an increased vulnerability to Alcohol Use Disorder.

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Age of Alcohol Initiation and Later Alcohol Outcomes

Large-scale epidemiological studies consistently report that individuals who initiate alcohol at earlier ages are four times more likely to experience an alcohol use disorder in their lifetime (Gruber, DiClemente, Anderson, & Lodico 1996). This vulnerability is not alcohol-specific, as early alcohol initiation is robustly related to illicit drug use, nicotine, and other substance use disorders as well as impulse control disorders, sexual risk behavior, early pregnancies and STDs, low educational achievement, and crime (Ellickson, Tuker, & Klein, 2003; Elliott, Huizinga, & Menard, 1989; Hajcak, Moser, Holroyd, & Simons, 2006; Hingson, Heeren, & Winter, 2006; King, Meehan, Trim, & Chassin, 2006; Stueve & O'Donnell, 2005). Current data suggest that the relationship between early alcohol initiation and later maladaptive outcomes is partially accounted for by a general underlying risk vulnerability (McGue, Iacono, Legrand, & Elkins, 2001; Prescott & Kendler, 1999). However, a preexisting common vulnerability does not entirely explain this relationship because it remains even after statistically controlling for multiple indicators of this risk, including, but not limited to, family history of alcohol and drug disorders, parent criminal conviction, socio-economic status, experience of maltreatment, parental and childhood intelligence, childhood under controlled temperament, and externalizing psychopathology (Grant & Dawson, 1998; Hawkins et al., 1997; Odgers et al., 2008).

A growing body of literature on the effects of alcohol in adolescence points to reward processes as potential mechanisms accounting for the relationship between early alcohol initiation and later maladaptive outcomes (Badanich, Maldonado-Devincci, & Kirstein, 2007; Maldonado-Devincci, Banadich, & Kirstein, 2010; Pascual, Boix, Felipo, & Gerri, 2009; Philpot & Kirstein, 2004; Philpot, Wecker, & Kirstein, 2009). Adolescent experimental organisms exhibited an increased sensitivity to the rewarding effects of alcohol but a decreased sensitivity to the negative effects of alcohol compared to adults (e.g.,

motor impairment, sedation, hangover symptoms; Nixon & McClain, 2010; Spear & Varlinskaya, 2005; Spear & Varlinskaya, 2010). Evidence has suggested that this could be due to the ongoing development of the mesolimbic dopamine system during adolescence but not adulthood (Chambers, Taylor, & Potenza, 2003). Age-related differences in vulnerability to alcohol appear within the adolescent period as well, such that early adolescents were more sensitive to alcohol-induced rewarding effects and less sensitive to alcohol-induced aversive effects than mid and late adolescents (Spear & Varlinskaya, 2005; Spear & Varlinskaya, 2010). This increased sensitivity to the positive effects of alcohol may be due to extant biological vulnerabilities unique to early adolescence, such as increased dopamine receptor levels in the reward centers of the brain (Teicher, Andersen, & Hostetter, 1995). Thus, it is likely that earlier ages of alcohol initiation are associated with increased alterations in reward processes after alcohol exposure than later ages of alcohol initiation.

Theory and Empirical Work on Repeated Alcohol Exposure and Reward Processes

Theories on repeated alcohol exposure and reward processes provide a framework for the pattern of responses that should occur at earlier ages of alcohol initiation. Although such processes are likely active throughout development, we expect them to be more pronounced at earlier ages of alcohol initiation. Theories on repeated alcohol exposure and reward processes, such as the Incentive Sensitization Theory (Robinson & Berridge, 1993), have argued that the sensitization of alcohol-related reward anticipation (increased positive emotions, arousal, and craving before receiving alcohol) and the desensitization of alcohol-related reward consummation (decreased positive emotions and arousal after receiving alcohol) play a significant role in repeated alcohol exposed individual's increased difficulty in reducing compulsive alcohol-seeking (Jentsch & Taylor, 1999; Lubman, Yücel, & Pantelis, 2004; Berridge & Robinson, 2003; Robinson & Berridge, 2001; Wiers et al., 2006). When presented with alcohol-related cues, individuals with repeated alcohol exposure displayed higher activity in reward centers of the brain (e.g., Ventral Striatum, Nucleus Accumbens; Kalivas & Stewart, 1991; Nestler, 1994; Self & Nestler, 1998; Koob & LeMoal, 1998), which have been linked with increased craving and risk for relapse (Heinz et al., 2014; Schneider et al., 2001). This heightened alcohol-related reward anticipation is thought to drive the cycle of alcohol use – "hijacking" the reward system and thus, biasing repeated alcohol exposure individuals to alcohol-related cues over general, conventional reward cues (Kalivas & Volkow, 2005;

Nesse & Berridge, 1997; Wrase et al., 2007). Given the heightened vulnerability of the brain during adolescence, it could be argued that these reward processes are even more severely impacted in individuals that initiated alcohol at earlier ages.

Researchers investigating how increased reward anticipation (e.g., positive arousal, positive emotions, and craving) develops in repeated alcohol exposure individuals have implicated reward learning as a potential mechanism (Conklin & Tiffany, 2002). According to learning theory (Conklin & Tiffany, 2002), an originally neutral stimulus (e.g., park) or another conditioned stimulus (e.g., peers) when regularly paired with alcohol will begin to produce the same effects of alcohol – thereby attaining the capacity to induce craving and pleasant feelings in and of themselves without alcohol being present (i.e., a conditioned response). For instance, animal work has discovered that, even after the pairing of neutral cues (e.g., lights) with alcohol was extinguished, animals still exhibited alcohol-seeking behaviors (Bienkowski, Kostowski, & Koros, 1999; Katner, Magalong, & Weiss, 1999). Furthermore, when presented with environmental cues that have been conditioned with alcohol, human subjects have reported increased craving for alcohol (Litt & Cooney, 1999). Given the salience of these environmental cues, formerly neutral or other conditioned stimuli become a part of a large network of factors that trigger reward anticipation for alcohol's positive effects. Importantly, the speed at which the network is built is thought to be increased in individuals with more severe alcohol exposure. This effect likely stems from alcohol's pharmacological effects, including increased phasic dopamine signaling to cues associated with alcohol (Hyman, Malenka, & Nestler, 2006; Spoelder, Tsutsui, Lesscher, Vanderschuren, & Clark, 2015). Like alcohol-related reward anticipation and consummation, it is possible that deficits in alcohol-related reward learning are more pronounced at earlier ages of early alcohol initiation (Spoelder et al., 2015).

Despite the appeal of repeated alcohol exposure theory and empirical work, it is still largely unknown how these processes, reward anticipation, consummation, and learning, unfold at earlier ages of alcohol initiation, given the lack of human studies. That is, do we see a greater degree of decoupling of alcohol-related reward anticipation (increased levels) and reward consummation (decreased levels) at earlier ages of alcohol initiation? Is the speed of alcohol-related learning increased at earlier ages of alcohol initiation? And what happens to general reward processes at earlier ages of alcohol initiation?

Empirical Work on Earlier Ages of Alcohol Initiation and Reward Processes

Although no human work has examined the intersection of reward processes and age of alcohol initiation, extant animal work on adolescent alcohol exposure and alcohol-specific reward processes has followed a similar pattern to repeated alcohol exposure individuals. Specifically, adolescent rats that were exposed to alcohol, compared to rats who were not, exhibited a greater ability to learn that pressing a lever resulted in alcohol, had higher rates of responding, exhibited a heightened resistance to extinguish alcohol-seeking behavior, and had higher craving-like behavior for alcohol (McBride, Bell, Rodd, Strother, & Murphy, 2005; Rodd-Henricks et al., 2002a). Importantly, through a similar experimental paradigm, researchers have discovered that adult rats exposed to alcohol did not show a similar pattern (i.e., no differences in alcohol-related learning, no increased craving behaviors for alcohol; Rodd-Henricks et al., 2002b), suggesting that timing of drinking episodes greatly impacts alterations in alcohol-related reward processes. However, whether earlier ages of alcohol initiation decrease alcohol-related reward consummation remains unknown. Despite this gap, overall, the animal literature has suggested that increased alcohol-related reward learning and anticipation may depend on age, rather than a pharmacological effect alone.

Additionally, animal work has supported increased sensitization of general reward anticipation processes as well. Specifically, adolescent rats with early alcohol initiation, compared to controls, exhibited higher basal dopamine levels, alterations in the mesolimbic dopamine system, and higher extracellular dopamine levels (Badanich, Maldonado-Devincci, & Kirstein, 2007; Maldonado-Devincci, Badanich, & Kirstein, 2010; Pascual, Boix, Felipo, & Guerri, 2009; Philpot & Kirstein, 2004; Philpot, Wecker, & Kirstein, 2009). Furthermore, at the behavioral level, rats exposed to alcohol during adolescence showed heightened generalized risk and novelty preference (Masse & Tremblay, 1997; Nasrallah, Yang, & Bernstein, 2009; Stewart, McGonnell, Wekerle, Adlaf, & MAP Longitudinal Study Research Team, 2011; Stansfield & Kirstein, 2007). However, the relationship between age of alcohol initiation and general reward learning is unknown and like alcohol-related reward consummation, no empirical work has investigated the relationship between age of alcohol initiation and general reward consummation.

Overall, animal work has suggested more pronounced deficits across the spectrum of alcohol-specific reward processes at earlier ages of alcohol initiation (e.g., increased alcohol-specific reward

learning, increased alcohol-specific reward anticipation). These findings are in line with theory on repeated alcohol exposure individuals. In terms of general reward processes, theory would predict desensitization of general reward anticipation but no differences in general reward learning or consummation after repeated alcohol exposure (Robinson & Berridge, 1993; Wrase et al., 2007). Limited animal work seems to suggest the opposite, with enhanced general-related reward anticipation at earlier ages of alcohol initiation; however, this may be due to animal researchers using control groups as a comparison group in general reward paradigms, instead of later alcohol exposed rats (Badanich et al., 2007; Maldonado-Devincci et al., 2010; Pascual et al., 2009; Philpot & Kirstein, 2004; Philpot et al., 2009). Therefore, more work is needed that explores both general and alcohol-specific reward processes at earlier ages of alcohol initiation; this would help to determine if reward mechanisms play a role in the increased risk for alcohol use disorders as well as general risk related behaviors in individuals that initiated alcohol at earlier ages.

Measurement of Reward Processes in Humans

To determine the interplay of reward processes in early alcohol initiators, research in humans is needed. To date, the Monetary Incentive Delay (MID) task is the most validated task for examining the different components of reward in relation to psychopathology (Knutson, Adams, Fong, & Hommer, 2001; Figee et al., 2012; Juckel et al., 2006; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008). In the MID task, the individual must, first, learn the cue and reward parings, with each cue serving as a signal for a certain magnitude of reward (learning phase). After this learning phase, there is a win cue that signals the opportunity to gain money or a neutral cue (anticipatory phase); then, there is a target that the participant must respond to as quickly as they can. Following the response, feedback is given and the monetary reward is presented, if the individual was quick enough (consummation phase). Most of the work with the MID task and reward has been conducted using functional Magnetic Resonance Imaging. Importantly, researchers have shown that separate brain circuits are activated during the reward anticipation (e.g., ventral striatum) and reward consummation (e.g., ventromedial frontal cortex) phases in the MID task (Knutson, Fong, Adams, Varner, & Hommer, 2001; Rademacher et al., 2010); therefore, supporting theories that argue for their discrete mechanisms in the brain (e.g., Incentive Sensitization Theory; Robinson & Berridge, 1993).

In addition to functional Magnetic Resonance Imaging, researchers have used electroencephalography (EEG) to dissociate the reward processes during the MID task and discovered that the MID task reliably produces Event Related Potentials (ERPs) at the various stages of reward processing (Broyd et al., 2012; Pornpattananangkul & Nusslock, 2015). Given the enhanced temporal resolution of EEG, it has an advantage over functional Magnetic Resonance Imaging, due to its capacity to examine all reward components in one task design. During reward anticipation, P3 has garnered the most theoretical and empirical support for being part of the anticipatory reward process (Broyd et al., 2012; van Boxtel, & Böcker, 2004). P3, a positive, centro-parietal wave occurring 300 – 600 ms after the cue, is thought to reflect reward categorization, with larger amplitudes being attributed to increased motivational salience to the cue (Pornpattananangkul & Nusslock, 2015). P3, unlike other anticipatory waves (e.g., Stimulus Preceding Negativity), was uncorrelated with consummatory ERPs; therefore, P3 showed the most promise as an index of reward anticipation cue (Pornpattananangkul & Nusslock, 2015).

During reward consummation, researchers have mainly focused on P3 and Late Positive Potential (LPP; Horan, Wynn, Kring, Simons, & Green, 2010; Lang & Bradley, 2010). The P3, as described above, also occurs in response to feedback and is thought to reflect reward evaluation (Horan, Wynn, Kring, Simons, & Green, 2010), with larger amplitudes being associated with increased magnitude of reward (Pornpattananangkul & Nusslock, 2015). The LPP is thought to reflect activity in the occipital and parietal cortices, which both have projections from the amygdala (Broyd et al., 2012). The LPP is also correlated with self-reported rating of emotional arousal and sympathetic arousal (Lang & Bradley, 2010; Broyd et al., 2012; Hajack, MacNamara, & Olvet, 2010). Given this, both feedback-P3 and LPP show promise theoretically as indices of the reward consummation process; notably, both are also uncorrelated with anticipatory reward ERPs (Pornpattananangkul & Nusslock, 2015). Although learning has not been examined in the MID task formally, it is possible to obtain a proxy behavioral index of reward learning by determining how accurately or quickly the participant can associate the anticipatory cue with the specified reward amount. The development of the MID and similar tasks has allowed researchers to measure the neural mechanisms underlying psychopathology in humans. This task would be informative when examining the effects of repeated alcohol exposure by age, as alterations in general and alcohol-related reward processes are expected to be even greater at earlier ages of alcohol initiation.

Limitations

Despite the wealth of literature suggesting that earlier ages of alcohol initiation are associated with an increased likelihood of developing alcohol use disorders (Dawson, Goldstein, Chou, Ruan, & Grant, 2008; Gonzalez, 1983; Gruber et al., 1996; Haertzen, Kocher, & Miyasato, 1983), there has been a lack of careful biobehavioral research on the potential role of reward processes. In humans, there have been no studies, to our knowledge, directly examining earlier ages of alcohol initiation and reward processes. In animals, research has revealed heightened general and alcohol-specific reward anticipation and heightened alcohol-specific learning; however, like in humans, reward consummation has not been examined. Thus, across both levels of analysis, there has yet to be a comprehensive study that has examined alcohol-specific and general reward processes in terms of anticipation, consummation, and learning. These are notable gaps given that current theories, such as the Incentive Sensitization Theory, on addiction could be greatly enhanced by knowledge regarding how earlier ages of alcohol initiation affect the pattern of reward processes.

Current Study

In the current study, we explored the relationship between age of alcohol initiation with general and alcohol-specific reward anticipation, consummation, and learning. For the general reward task, we used neutral anticipatory cues (i.e., various circles) to signal a specific reward amount; in the alcohol reward task, we used alcohol anticipatory cues (i.e., various alcohol drinks) to signal a specific reward amount. For reward anticipation, we were focused on cue-P3 to the neutral and win cues. For reward consummation, we focused on feedback-P3 and feedback-LPP to the neutral and win feedback. It is important to note that it is very difficult to get a pure index of reward learning. At the behavioral level, how quickly an individual learns that a cue means a specific reward is tied to reward anticipatory processes as well. In the current study, we used this behavioral index in an attempt to obtain the most comprehensive insight into reward learning. Although this is not strictly a learning index, this is how reward-related learning would work in the real-world.

Notably, several genetic and environmental variables have been associated with earlier ages of alcohol initiation including: age, gender, ethnicity, socioeconomic status of parents before drinking onset, Antisocial Personality Disorder symptoms, alcohol use symptoms, family history of alcohol and drug use,

parental monitoring before drinking onset, popularity before drinking onset, deviant peers before drinking onset, childhood neglect, and childhood abuse (Donovan, 2004; Dube et al., 2006; Flory, Lynam, Milich, Leukefeld, & Clayton, 2004; Grant, Stintson, & Harford, 2001; Gruber et al., 1996; Hawkins, Catalano, & Miller, 1992; Kaplow, Curran, & Dodge, 2002; Killen et al., 1996; Kosterman, Hawkins, Guo, Catalano, & Abbott, 2000). To ensure that age of alcohol initiation predicts reward processes, beyond these covariates, we explored the relation of age of alcohol initiation with reward processes before and after controlling for relevant covariates.

Drawing on animal empirical work, we hypothesized that earlier ages of alcohol initiation would be associated with increased alcohol-related reward anticipation (cue-P3) and increased general reward anticipation (cue-P3). Additionally, we hypothesized that earlier ages of alcohol initiation would be associated with increased alcohol-related reward learning but show no association with general reward learning. Given theory and work on the effects of repeated alcohol exposure, we hypothesized that early alcohol initiation would be associated with decreased alcohol-specific reward consummation (feedback-P3 and feedback-LPP) but show no decrease in general reward consummation (feedback-P3 and feedback-LPP). In all analyses, we controlled for all relevant genetic and environmental covariates identified in the previous literature.

Method

Participants

123 participants (74% Female; 55% Caucasian; M_{Age} = 20.38) were recruited thorough the University of South Florida Department of Psychology participant pool and completed both parts of the study. The inclusion criteria included the following: can read and write in English; right-handed; no history of a neurological disorder; no history of medications that impact the dopaminergic system (e.g., Adderall); have drank alcohol in the past three months; and have not drank alcohol in the past 72 hours. Participants (N = 1) that had a positive screen for psychosis during the structured clinical interview in part 1 were excluded from part 2 of the study. Additionally, participants (N = 15) that dropped out after completing part 1 were excluded from analyses. Notably, the individuals that dropped out were not statistically different from the included participants on our key variable of interest, age of alcohol initiation, on alcohol use disorder symptoms, or frequency of alcohol use. The final sample consisted of 123 current college drinkers with a mean of 16.02 years old on age of alcohol initiation (SD = 2.39), with a mean of 2.59 on Alcohol Use Disorder Symptoms (SD = 2.32), with a mean of 3.89 (SD = 1.61) on past 30 day alcohol use and thus, qualitatively between “two days per month” and “three days per month”, and with a mean of 3.86 (SD = 1.11) on past 6 month alcohol use and thus, qualitatively between “once a month” and “2-3 times per month” (see below in Characterization of Participants for scaling of the alcohol use frequency variables). The University of South Florida Institutional Review Board approved all procedures prior to study initiation.

Measures

Potential Covariates

Characterization of Participants. A brief self-report questionnaire was administered to obtain information on gender, age, and ethnicity. Additionally, frequency of past 30 days alcohol use and past 6 month alcohol use was assessed through two items. These questions were: how often have you drank

alcohol in the past 30 days? (1 = no use, 2 = one day, 3 = two days, 4 = three days, 5 = once a week, 6 = two to three days per week, 7 = four to six days per week, 8 = once a day per week, and 9 = more than once a day) and how often have you drank alcohol in the past 6 months? (1 = no use, 2 = less than once a month but at least once in the last 6 months, 3 = once a month, 4 = two to three times per month, 5 = once or twice per week, 6 =three to four times per week, and 7 = nearly every day). These items were administered in part 1 of the study.

Psychopathology. The Mini-International Neuropsychiatric Interview-7 (M.I.N.I.-7; Sheehan et al., 1998) is a short diagnostic interview that assesses DSM-V disorders. An independent rater coded all interviews; in the case of a discrepancy, the consensus was reached through the assistance of a PhD level clinician. For the purposes of the current study, only Alcohol Use Disorder and Antisocial Personality Disorder modules were used. This was administered in part 1 of the study.

Socioeconomic Status. Socioeconomic status (SES) was assessed through two items: What was your mother and father's combined annual household income when you were in middle school? And What was your mother and father's combined annual household income when you were in high school?. The following scaling was used: 1 = $0 – $49,000, 2 = $50,000 – $99,000, 3 = $100,000 – $149,000, and 4 = greater than $150,000. The data for SES was analyzed based on their age of first drink, with the more proximal SES to age of first drink used. This was administered in part 1 of the study.

Family History of Alcohol and Drug Abuse. The Family History Assessment Module (FHAM; Rice et al., 1995) is a 30-minute structured interview that asks screening questions about familial history of psychiatric illnesses. For example, the screening question for alcohol dependence is, "have any of your relatives ever had any family job, school, police, or health problems because of drinking?". For the purposes of the current study, only questions pertaining to familial history of alcohol and drug use were administered. If the participant reported a relative with a history of alcohol or drug problems, the Individual Assessment Module (IAM; Rice et al., 1995) was administered. The IAM assessed for alcohol dependence and substance dependence diagnostic symptoms per the DSM-III-R (i.e., > 3 symptoms). Two composite scores were calculated, a sum score of the number of family members with an Alcohol Dependence and a sum score of the number of family members with Substance Dependence. An independent rater coded all interviews. In the case of a discrepancy, the consensus was reached through

the assistance of a PhD level clinician. The FHAM and IAM informant responses have demonstrated a specificity and sensitivity with the relative's report of symptoms of 98% and 39% respectively.

Childhood Trauma. The Childhood Trauma Questionnaire-Short Form (CTQ-SF; Bernstein et al., 2003) is a 28-item scale that measures childhood maltreatment experiences through a five-point scale ranging (1 = never true to 5 = very often true). The scale targets physical, sexual, and emotional abuse as well as physical and emotional neglect. Sample items include: "Someone tried to touch me in a sexual way, or tried to make me touch them," "People in my family hit me so hard that it left me with bruises or marks," and "I thought that my parents wished I had never been born." A total scale score of abuse and neglect was calculated for the purposes of the current study. The CTQ-SF has demonstrated good test-retest reliability (r = .86; Bernstein & Fink, 1998). In the current study, the internal consistency for the total abuse and total neglect composite scores was .89 and .86 respectively. This was administered in part 1 of the study.

Peer Influence. The Friends Inventory (Walden et al., 2004) is a 26-item questionnaire that measures peer deviance. It asks on a 4-point scale (1 = none of my friends are like that to 4 = all of my friends are like that) how much the statement describes their friends. It contains two subscales: peer substance use and peer delinquency. Sample items include: "My friends drank alcohol or beer" and "My friends broke the rules." Strong validity and reliability (*a* = .82 - .88; Walden et al., 2004) of the scale have been established. A composite score of the two subscales was calculated in the current study given the high correlation. The internal consistency was .82 for the composite peer deviance index. This was administered in part 1 of the study.

Parental Monitoring. Monitoring was assessed through the composite score of three items that we have adapted to account for age at which they initiated alcohol (Chassin, Pillow, Curran, Molina, & Barrera, 1993). Participants were asked, to what extent, their parents discussed with them their daily plans before they initiated alcohol use, have knowledge of their interests and activities before they initiated alcohol use, and know about their whereabouts and the identity of their associates when they were not at home before they initiated alcohol use. Internal consistency (*a* = .53 - .83; Dick et al., 2007) for this scale has been established, and was.81 in the current study. This measure was administered in part 1 of the study.

Popularity. Since there are not well-established measures to assess popularity, it was assessed through two items: How popular were you with girls in the year before you initiated alcohol use? And how popular were you with guys in the year before you initiated alcohol use. They were given a 7-point scale for these items (1 = not popular and 7 = very popular). We created a composite score for these two items due the strong correlation (r = .82) between the items in the current study. This was administered in part 1 of the study.

Main Variables of Interest

Age of Alcohol Initiation. Age of alcohol initiation was determined through the following question: "At what age did you first drink alcohol beyond a sip or a taste?". This was administered in part 1 of the study.

General Reward Processes. The Monetary Incentive Delay-General task (MID-General; Broyd et al., 2012; Knutson et al., 2001; see *Figure A1*) is a task that assesses reward processes. Before the task begins, participants were shown the money that they can earn ($10) by performing the task successfully, and the money was left in front of the participants on the table. In this task, there were cues that signaled potential gain of reward or no reward. Four cues signaled potential reward (denoted by different circles), varying in magnitude (i.e., a circle with a horizontal line = 20 cents; a circle with two horizontal lines = 40 cents; a circle with one vertical lines = 1 dollar; a circle with two vertical line = 5 dollars). One cue signaled no monetary reward (denoted by a triangle), that served as a neutral condition.

Typically, in the task, there are practice trials to ensure the participant understands the association between cues and rewards. To get a behavioral index of learning, we presented each cue and then, asked the participant how much it is worth (multiple choice format). The cues were randomized in each block, with 10 blocks total, and participants were told whether they were correct or not. This terminated after 10 blocks. After this, 10 practice trials occurred.

For each trial, participants saw one of five cues (250 milliseconds). Then, they fixated on a cross for a variable amount of time (1600 to 2000 milliseconds). After this, the participant responded to a target square that was shown for a variable amount of time (started at 300 milliseconds) with a button press. The target square display time was determined through an adaptive algorithm, such that speed was increased by 33 milliseconds if the individual was not fast enough for the same cue on the previous trial

or was decreased by 25 milliseconds if the individual was fast enough for the same cue on the previous trial. This resulted in approximately a 66% win rate across subjects. Feedback (1500 milliseconds) followed the button press. During gain cues, participants were told that they can win money by pressing the “1” key as fast as they can when the target comes up. In the gain condition, they were told that a fast response resulted in positive feedback and money. After the practice trials, the participants were administered the experimental trials (3 experimental blocks of 55, with 5 minute breaks in between). This was administered in part 2 of the study.

Alcohol-Specific Reward Processes. The alcohol-specific MID (MID-Alcohol; see *Figure A2*) task was adapted from the General-MID. All elements in the adapted task remained the same as described above, instead of neutral cues, there were standard pictures of alcohol. In place of the circles (denoting reward) and triangle (denoting no reward), there was varying pictures of mixed drinks (denoting reward) and a glass of coke (denoting no reward). Since alcohol preference may be a relevant covariate, after the study, we assessed how much they liked the drink in the presented cue (1 = do not like at all and 5 = very much like). This was administered in part 2 of the study.

Measurement of Neural Data

Electroencephalography. EEG data were collected through 128 electrode Geodesic Sensor Nets (Electrical Geodesics, Inc., Eugene, OR). EEG data were acquired throughout the study at a sampling rate of 250 Hz with .1-100 Hz analog filtering. To further reduce noise, data were filtered offline with a lowpass of 20 Hz.

Procedure

Participants volunteered to participate in the proposed study through an online participant pool, SONA. The study consisted of two parts (see *Figure B1*). For part 1, eligible and consenting participants came into the lab to complete self-report questionnaires and the structured interviews. Upon completion, they were told to sign up for part 2 of the study. Only participants that completed part 1 could participate in part 2 of the study.

Once the participants signed up for part 2, they were instructed to come to the lab. Upon arrival, the EEG was set up for data acquisition. The appropriate EEG net was determined by measuring the width of the participant’s head. Electrodes were soaked in salt water prior to being fitted on the

participant's head. The participant was instructed to not chew any gum for the duration of the experiment and to remove their cell phone from their pocket. After the EEG net was properly placed, participants were hooked into the EEG net amplifier in the experimental room. After this, the research assistant ensured that the impedance was in the acceptable range. If any electrodes were identified as having high impedance, research assistants soaked the electrode in additional salt water and made sure there was direct contact with the skin. Through the entirety of the experiment, the research assistant monitored impedance to ensure the accuracy of the data. After the EEG was properly set up, the behavioral tasks were administered. The order of the tasks were counterbalanced across participants and a 5 minute break was provided between tasks.

Results

Preliminary Analyses

Normality. All variables were explored for evidence of problematic skewness (beyond the -2 to +2 range). The only variable that exceeded this range was Antisocial Personality Disorder symptoms, with an original skewness of 4.17; after a square root transformation, the skewness was reduced to 2.50. The square root-transformed Antisocial Personality Disorder variable was used across relevant analyses. Univariate outliers were determined if they exceeded the +/- 2*IQR. All outliers were replaced with a value of +/- 2*IQR. All results presented below were replicated with outliers.

Behavioral learning data. Reward learning was calculated by determining the percentage of trials where the individual correctly paired the cues; namely, mixed alcohol drinks (alcohol reward learning) or neutral circle cues (general reward learning), with the specific monetary amount.

ERP Analysis. For cue-P3 and feedback P3 and LPP (see *Figure C1* for electrode montage), stimulus-locked EEG data were segmented offline into 1000 ms epochs. For cue-P3, this was 200 ms before of the anticipatory cue and 800 ms after the anticipatory cue was presented; for feedback P3 and LPP, this was 200 ms before feedback and 800 ms after feedback. The EEG segments were screened and corrected for artifacts (e.g, eye blinks, head movement) using EGI's Net Station Artifact Detection Software. We had a delay of 10ms from the event marker to when the participant saw the stimuli. Therefore, in all analyses, we corrected for a 10 ms offset.

After cleaning, each epoch was sorted based on task and was averaged to create the subject's cue-P3 (300 – 450 milliseconds after the cue), feedback-P3 (300 – 450 milliseconds after feedback), and feedback-LPP (450 – 600 milliseconds after feedback) for the neutral condition and for the win condition. Each ERP summation was corrected to account for baseline. Given the problems with difference scores, each subject's neutral activity to the cue and feedback were controlled for in all relevant analyses.

Covariate Analyses

The following covariates were explored in relation to age of alcohol initiation: age, gender, ethnicity, socioeconomic status of parents before drinking onset, Antisocial Personality Disorder symptoms, alcohol use symptoms, family history of alcohol and drug use, parental monitoring before drinking onset, popularity before drinking onset, deviant peers before drinking onset, childhood neglect, and childhood abuse. Antisocial Personality Disorder symptoms (r = -26; $p < .05$), family history of drug use (r = -.20; $p < .05$), deviant peers before drinking onset (r = -.41; $p < .05$), childhood neglect (r = - .20; $p < .05$), and childhood abuse (r = -.38; $p < .05$) were all significantly related to age of alcohol initiation.

The following covariates were explored in relation to our neural (i.e., P3 to cue and P3 and LPP to feedback) and behavioral indices (i.e., learning accuracy): the extent of which the individual believed they were going to win money, mean pleasure ratings for the money feedback, mean pleasure ratings for the alcohol pictures, use of nicotine products before the experiment, and mean ratings for motivation for money. The only significant relation for these variables was between mean ratings for money motivation and general learning accuracy (r = .22; $p < .05$). These significant covariates were controlled for in all relevant analyses.

Order Effect and Manipulation Check

Although the behavioral tasks were counterbalanced across participants, evidence of order effects was explored in relation to our neural and behavioral indices. There was a significant order effect for the MID-A task [F = 14.22; $p < .05$] on alcohol learning accuracy; therefore, in analyses involving alcohol learning accuracy, order was controlled for. There was no further evidence of order effects with our other dependent variables.

Frequency and descriptive analyses were conducted to determine the extent to which participants were engaged and motivated in the tasks. Participants were asked, before they received their monetary reward, whether they believed they were going to win money based on their performance on the task; 44% said “yes,” 33% said “kind of,” and 10% said “no.” Participants reported an average score of 4.55 (1 = not at all motivated and 6 = extremely motivated) when assessing their motivation to win the money during the tasks. When asked to what extent they found monetary feedback rewarding (1 = not at all rewarding and 6 = extremely rewarding), participants rated the monetary feedback as a 4.11 overall, with $5 exhibiting the highest rating at a 5.64; participants rated the alcohol cues as a 3.84 overall. These data

suggest that the participants, for the most part, believed they could win the money and found the cues and feedback rewarding.

Repeated measure ANOVAs for our MID-Alcohol and MID-General tasks were conducted to determine the overall effect of win conditions compared to neutral conditions on our neural indices. For the MID-Alcohol task, the win condition resulted in significantly increased cue-P3 [M_{win} = 4.52; $M_{neutral}$ = 3.60*;* F = 12.11; p < .05], feedback-P3 [M_{win} = 3.47; $M_{neutral}$ = 2.42*;* F = 6.38; p < .05], and feedback-LPP [M_{win} = 2.52; $M_{neutral}$ = 1.14; F = 7.67; p < .05] amplitudes when compared to neutral trials. Therefore, the task reliably produced anticipatory and consummatory waves in response to the cue and feedback respectively. Unexpectedly, the win condition for the MID-General, when compared to the neutral condition, was not significantly higher in mean amplitude for cue-P3 (M_{win} = 2.06; $M_{neutral}$ = 1.41), feedback-P3 (M_{win} = 2.94; $M_{neutral}$ = 2.91), or feedback-LPP (M_{win} = 3.36; $M_{neutral}$ = 3.00).

Effect of Age of Alcohol Initiation on Reward Components

Multiple linear regressions between age of alcohol initiation and our reward indices, before controlling for covariates, were conducted. For all analyses involving ERP components, the neutral activity to the cue/feedback was controlled for. Age of alcohol initiation was significantly and positively correlated with alcohol-related reward consummation for both feedback-LPP (r = .21; p < .05) and feedback-P3 (r = .24; p < .05). Additionally, age of alcohol initiation was significantly and negatively associated with alcohol-related reward learning (r = -.20; p < .05; see *Figure 1*). Age of alcohol initiation was not associated with alcohol-related reward anticipation or any general reward processes.

Multiple linear regressions were conducted with relevant genetic and environmental covariates in step 1 and age of alcohol initiation in step 2 predicting reward cue-P3, feedback-P3, feedback-LPP, and reward learning for the MID-General and MID-Alcohol tasks (see Table D1)[1],[2]. The results were in line with the bivariate correlational analyses. Contrary to our initial hypotheses, there were no significant

[1] Given that repeated alcohol exposure may be conflated with our age of alcohol initiation variable, we also explored the moderating effect of alcohol use disorder symptoms on the relationship between age of alcohol initiation and reward processes, in addition to controlling for it in the analyses presented above. None of these moderation effects were significant.

[2] We also collected information on who the individual first drank with (friends versus parents) as well and explored the moderating effect of presence of friends on the relationship between age of alcohol initiation and reward processes. None of these moderation effects were significant.

relationships between alcohol initiation and cue-P3 for the alcohol reward task (*B* = -.05) or the general reward task (*B* = .09). Therefore, age of alcohol initiation was not associated with more pronounced changes in general or alcohol-specific reward anticipation. In line with our initial predictions, age of alcohol initiation was significantly and negatively associated with alcohol-reward learning accuracy (*B* = -.28; *p* < .05), and explained an additional 5% of the variance beyond our relevant covariates. However, age of alcohol initiation was not significantly associated with general reward learning (*B* = .04). This suggests that heightened reward related learning at earlier ages of alcohol initiation may be alcohol-specific.

Additionally, in line with our initial predictions, age of alcohol initiation was significantly and positively associated with our reward consummation indices, feedback-P3 (*B* = .19; *p* < .05; see *Figure D1*) and feedback-LPP (*B* = .24; *p* < .05; see *Figure 2 and Figure D2*), during the alcohol task and explained an additional 4-5% of the variance beyond relevant covariates for both analyses. There was not a significant relationship between alcohol initiation and feedback-P3 (*B* = -.02) or feedback-LPP for the general reward task (*B* = -.01). These results suggest that earlier ages of alcohol initiation may reduce reward consummation (arousal, positive emotions) to alcohol-related reward but not general reward.

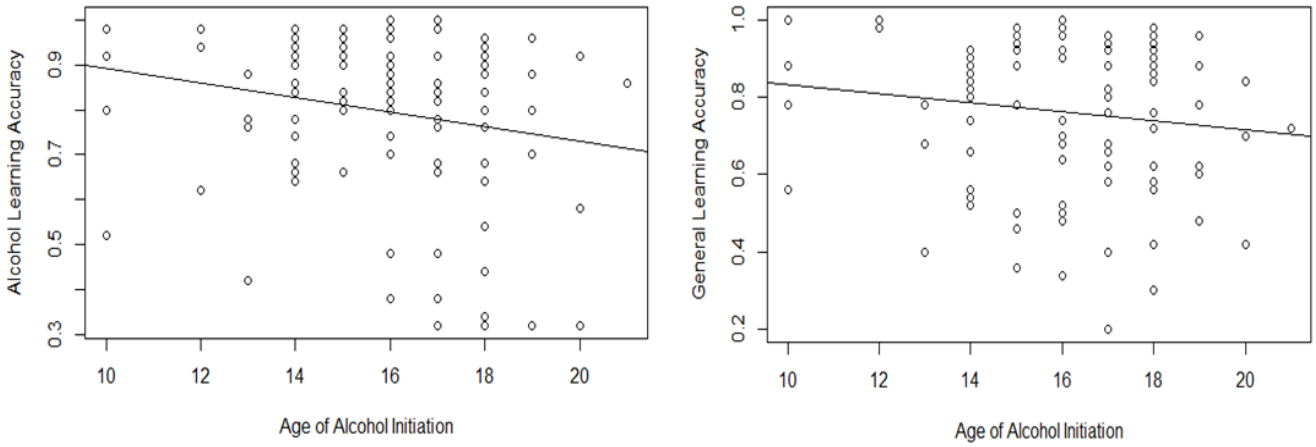

Figure 1. Scatterplots of the Effect of Age of Alcohol Initiation on Learning

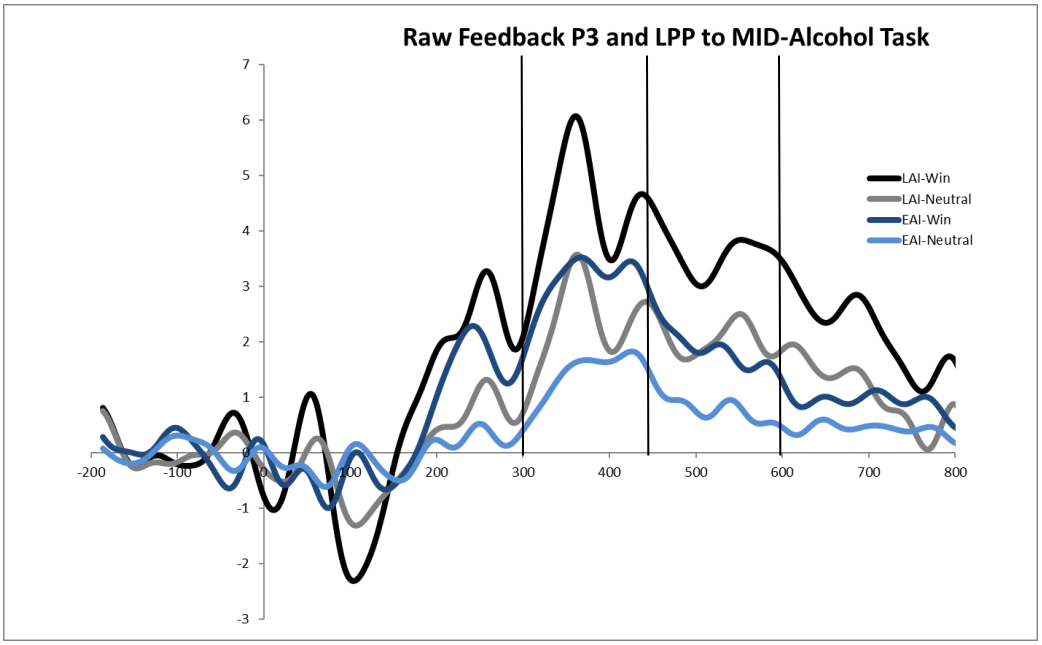

Figure 2. The Effect of Alcohol Initiation on Alcohol Feedback P3 and LPP. The vertical lines in the graphs represent the time windows for P3 and LPP. A median split was conducted on age of alcohol initiation only for graphing purposes.

Discussion

The current study provides the first simultaneous neural and behavioral examination in humans of the relationship between age of alcohol initiation and alcohol-specific and general reward processes, beyond several genetic and environmental covariates. In line with our initial predictions, earlier ages of alcohol initiation were associated with increased alcohol-related learning but not for general reward learning. Additionally, in line with our initial predictions, earlier ages of alcohol initiation were associated with decreased alcohol-related reward consummation (LPP and P3) but not for general reward consummation. Contrary to our initial predictions, age of alcohol initiation was not associated with alcohol-related reward anticipation (P3) before or after controlling for covariates or with general reward anticipation (P3) after controlling for covariates. Overall, this pattern of results suggests that earlier ages of alcohol initiation are associated with more pronounced deficits in alcohol-related learning and consummation only. These alcohol-specific reward processes represent potential mechanisms accounting for the relationship between earlier ages of alcohol initiation and increased risk of alcohol use disorders later in life.

In terms of alcohol-related reward learning, it could be argued that earlier ages of alcohol initiation foster a more rapid development of associative learning processes and a more rigid learning history due to the ongoing development of the mesolimbic dopamine system. This would need support from work that allows for more causal conclusions than in the current study. Nonetheless, this is certainly in line with animal work that showed a decreased ability to extinguish cue and alcohol associations as well as heighted dopamine signaling to alcohol cues during the adolescent period (Rodd-Henricks et al., 2002a; Spoelder et al., 2015). This heightened alcohol-related associative learning may be one of the underlying mechanisms accounting for the higher risk of alcohol use disorders at earlier ages of alcohol initiation, with early alcohol initiators showing a larger and more persistent network of factors that trigger alcohol-related reward anticipation. Heightened alcohol-related learning is likely the driving force behind the

increased risk for maladaptive patterns of drinking in early alcohol initiators, despite experiencing decreased consummatory effects (i.e., decreased arousal and pleasant feelings).

Our findings on the association between earlier ages of alcohol initiation and alcohol-related reward learning and consummation are in line with empirical work on repeated alcohol exposure (Hyman et al., 2006, Kalivas & Stewart, 1991; Nestler, 1994; Self & Nestler, 1998; Koob & LeMoal, 1998). They also extend current theory, such as the Incentive Sensitization Theory (Robinson & Berridge, 1993), by highlighting the importance of developmental time period when considering the effects of alcohol on reward alterations. The current findings also highlight the potential for alcohol-related reward learning and consummation to be underlying mechanisms accounting for the relationship between early alcohol initiation and a greater risk for alcohol use disorders, a question that has been examined in extant human literature. Prevention efforts to the delay onset of alcohol use, to offset a rigid and more prolific alcohol-related learning network, are needed.

Unlike alcohol-related reward learning and consummation, we failed to find more pronounced alterations in alcohol-related reward anticipation at earlier ages of alcohol initiation. This lack of significance is unexpected given work noting heightened P3 (an index of craving; Barthalow, Lust, & Tragesser, 2010) to alcohol images in repeated alcohol exposed individuals (Namkoong, Lee, Lee, Lee, & An, 2004) and given animal work that showed increased craving for alcohol (i.e., more lever-pressing) in adolescent but not adult rats (Rodd-Henricks et al., 2002b). Since there is a strong tie between P3 and motivational salience (Barthalow et al., 2010), our lack of significant findings is likely not due to ERP measurement issues. One potential explanation is that increased reward anticipation or craving for alcohol only occurs during certain motivational states (e.g., withdrawal, stress). This is in line with theories that argue for a Negative Reinforcement model of addiction, with physiological and feeling states driving reward anticipation for alcohol (Ahmed & Koob, 2005). Therefore, it is possible that the cues in the current study did not activate alcohol-specific reward anticipation due to the lack of negative physiological states. Future work testing the Negative Reinforcement model (Ahmed & Koob, 2005) of addiction against the Incentive Sensitization Theory (Robinson & Berridge, 1993) in early alcohol initiators is needed.

Another potential reason for the lack of significant findings in the current investigation but not in animal work may be due discrepancies in experimental paradigms between human and animal work.

Much of the animal literature has compared alcohol-exposed adolescents to controls, not allowing for a direct test of developmental time period (e.g., McBride et al., 2005; Rodd-Henricks et al., 2002a). Furthermore, in the limited studies that have (Rodd-Henricks et al., 2002b), the exposure to alcohol is not "natural"; instead, time windows are divided into categories (adolescent vs. adulthood), and rats are assigned to drinking conditions. In the current study, we treated age of alcohol initiation as a continuum, allowing for a more ecologically valid approach to testing the impact of development on alcohol exposure and reward processes. The current study does not stand alone in terms of an inability to replicate across levels of analyses. Indeed, researchers examining repeated alcohol exposure and reward processes in humans (Ostafin, Marlatt, & Troop-Gordon, 2010) have failed to replicate findings from the animal level implicating higher alcohol-related reward anticipation in repeated alcohol exposure individuals (Robinson & Berridge, 1993; Berridge & Robinson, 2003). Therefore, it may be that this is a design issue across levels of analysis as well. Future work in humans with neural and behavioral experimental designs should be conducted to determine if it is, indeed, due to the levels of analysis.

Similarly, we did not find a significant relationship between earlier ages of alcohol initiation and increased general reward anticipation. Similar to above, the source of the discrepancy likely lies in the differences between animal and human designs. Animal studies have used a non-drinking control group as a comparison to early alcohol initiators, instead of a later alcohol exposed group (Badanich et al., 2007; Maldonado-Devincci et al., 2010; Pascual et al., 2009; Philpot & Kirstein, 2004; Philpot et al., 2009). Therefore, although they found increases in general reward processes, it is unclear if this is due to age or simply the pharmacological effect. Another possibility is that our general reward paradigm was not a reliable index of reward anticipation and consummation, given the failed manipulation check of our neural indices, and thus, we were unable to detect effects. Replication studies for the general reward processes are needed to determine if it is the level of analysis that is driving the discrepancy or measurement issues in the current study.

The current study had several strengths. First, it provided the first experimental examination of all three general and alcohol-specific reward processes across human and animal work. The findings support and extend the Incentive Sensitization Theory (Robinson & Berridge, 1993) by showing that earlier ages of alcohol initiation may foster a greater sensitization in alcohol-specific reward-learning and

more pronounced decreases in alcohol-related consummation. Secondly, we controlled for an extensive list of covariates, allowing us to draw a strong experimental argument for the direct pharmacological effects of alcohol at earlier ages, rather than indirect effects of environment and genetics. Lastly, we found that repeated alcohol exposure effects and first contextual alcohol experiences (peers present or absent) did not moderate the relationship between age of alcohol initiation and alcohol-related reward processes. This allowed us to rule out the potential confounding effects of amount of alcohol exposure and first contextual alcohol experiences on the relationship between our variables of interest.

Despite these strengths, there a few limitations that should be addressed in future work. The current study relied on anticipatory pictures and consummatory feedback to target our reward processes of interest. Behavioral paradigms in the lab where the individual is primed with real-life alcohol cues (e.g., vodka bottle; reward anticipation phase) and then, afforded the opportunity to drink alcohol (reward consummation phase) would determine if the results generalize to the behavioral level. Additionally, longitudinal neural and behavioral designs targeting alcohol and general reward processes before and after drinking onset would provide a stronger case for causality. Furthermore, our lack of significant findings between earlier ages of alcohol initiation and general reward processes suggest that mechanisms (e.g., personality changes), other than reward processes, may be underlying the relationship between earlier ages of alcohol initiation and general risk taking behaviors. However, it may also be due to our general reward task indices not being a reliable measure of these processes. Future replication studies are needed as well as other studies that explore more potential mechanisms underlying the association between earlier ages of alcohol initiation and increased risk for maladaptive outcomes.

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APPENDIX A:

DEPICTION OF MEASURES

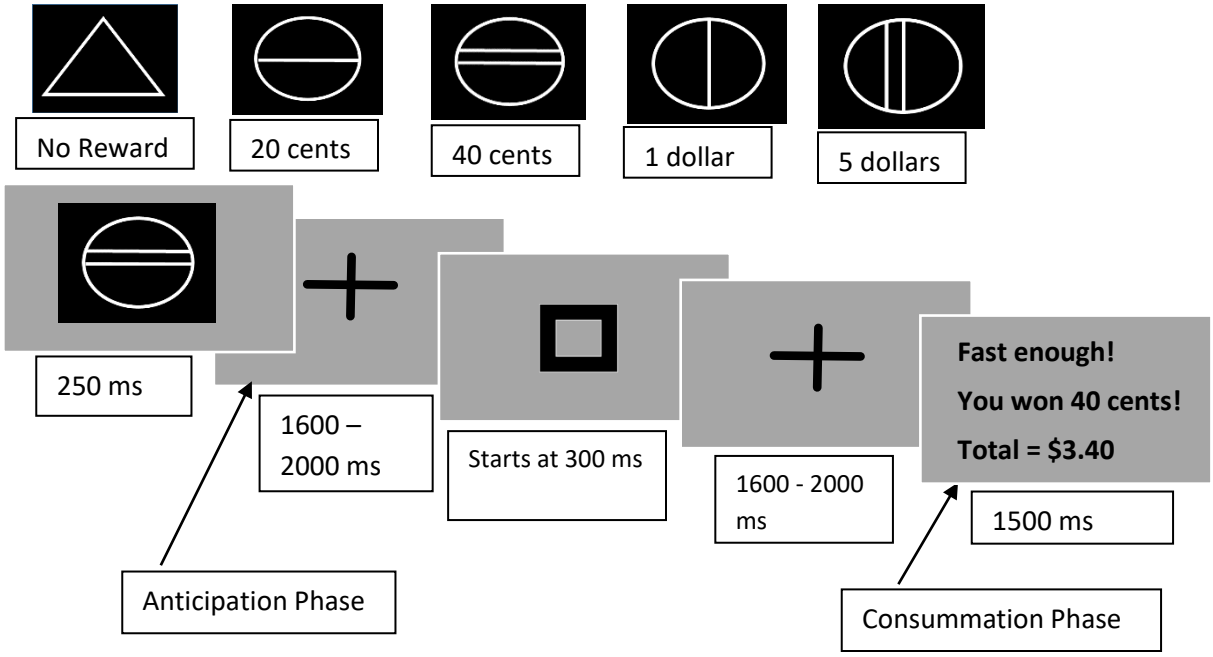

Figure A1: The General-MID task. The target square started at 300 milliseconds (ms); however, there was an adaptive algorithm, such that the timing was +33 ms on the previous trial time with the same cue if they were wrong (i.e., not fast enough) or -25 ms on the previous trial time with the same cue if they were right (i.e., fast enough). The algorithm produced roughly a 66% chance of winning.

APPENDIX A (CONTINUED):

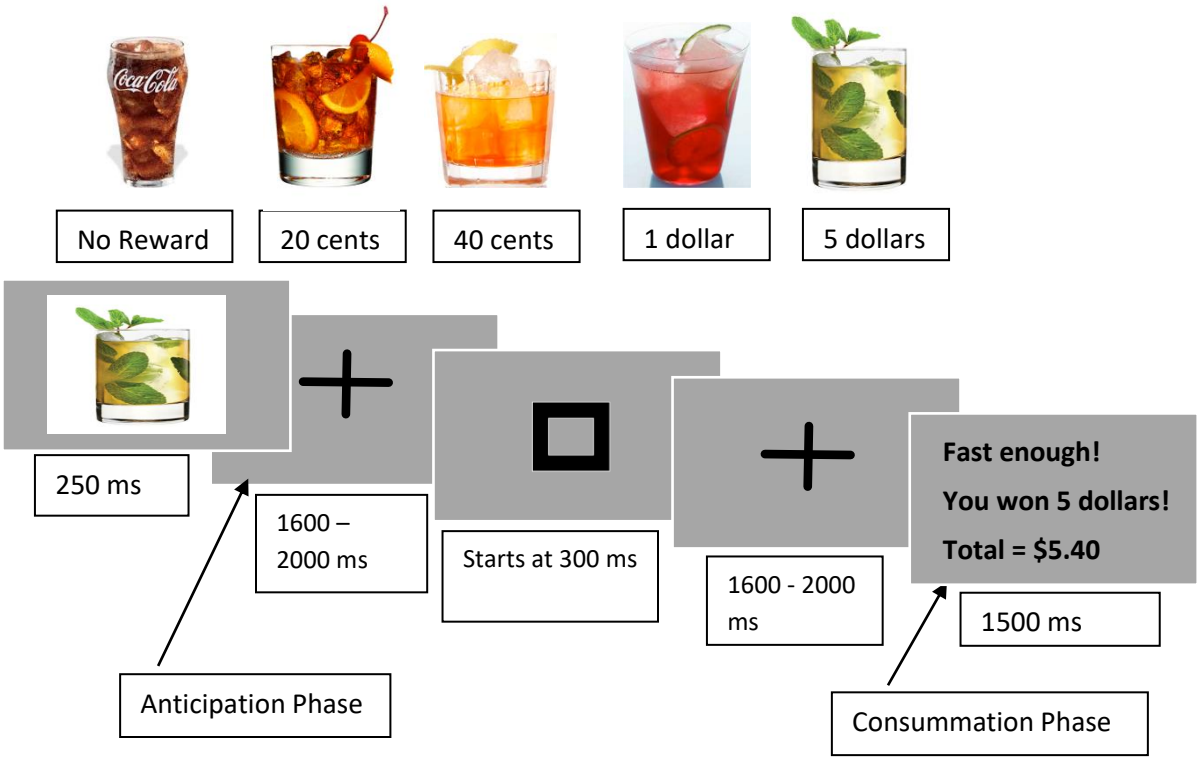

Figure A2: The Alcohol-MID Task. The target square started at 300 milliseconds (ms); however, there was an adaptive algorithm, such that the timing was +33 ms on the participant's previous trial time with the same cue if they were wrong (i.e., not fast enough) or -25 ms on the previous trial time with the same cue if they were right (i.e., fast enough). The algorithm produced roughly a 66% chance of winning.

APPENDIX B:

STUDY PROCEDURE

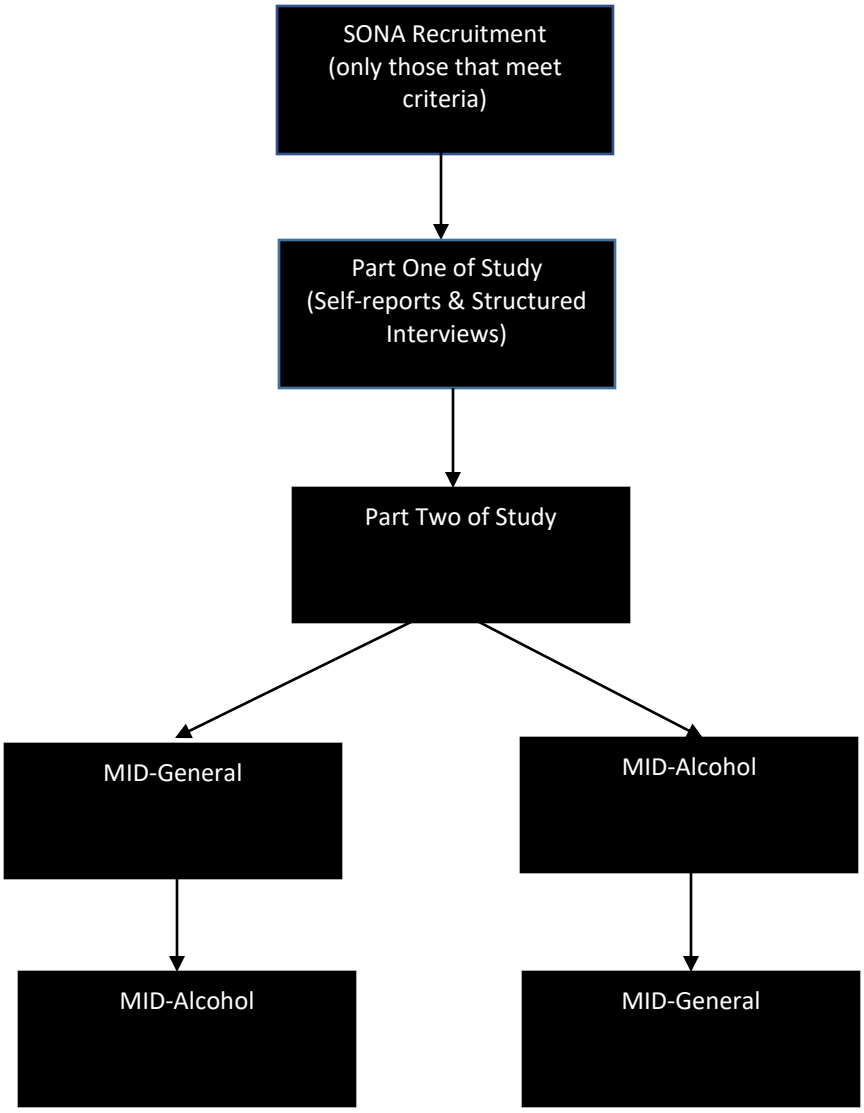

Figure B1: Study Procedure Outline.

APPENDIX C:

MONTAGE OF ELECTRODES

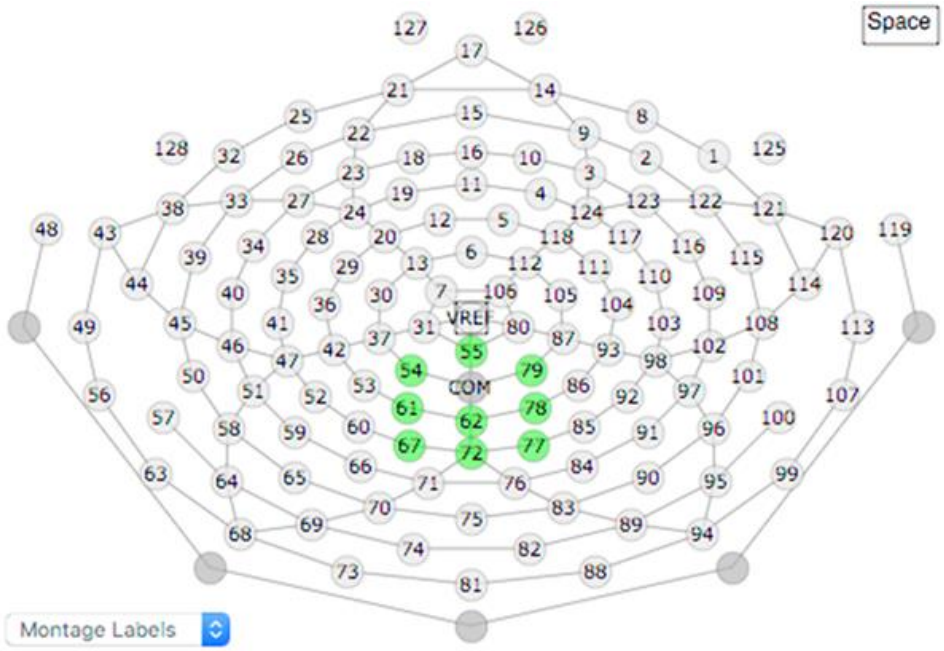

Figure C1: Montage for P3 and LPP. The montage of electrodes used to calculate Cue-P3 and Feedback-LPP for both the MID-Alcohol and MID-General tasks.

APPENDIX D:

Full Multiple Regression Results

Table D1. Multiple Regressions of Age of Alcohol Initiation on Reward Processes

	Alcohol Cue-P3	Alcohol Feedback-P3	Alcohol Feedback-LPP	Alcohol Learning	General Cue-P3	General Feedback-P3	General Feedback-LPP	General Learning
				β				
Step 1								
Neutral Cond	.59**	.41**	.37**	--	.35**	.34**	.17	--
ASPD Sx	.05	-.15	-.18	-.07	-.05	-.04	-.06	-.07
Familial Drug Use	-.01	-.05	.01	-.06	-.07	.02	.05	.09
Deviant Peers	.22*	-.09	.00	.00	.06	.00	.06	.06
AUD Sx	-.09	.07	.00	.15	-.14	.20	.20	.02
Childhood Abuse	-.04	.06	.03	-.11	.03	-.14	-.24	.12
Childhood Neglect	.08	-.12	-.16	.18	-.09	.15	.12	.04
Money Motivation	--	--	--	--	--	--	--	-.22
Alcohol Task Order	--	--	--	.26*	--	--	--	--
				β				
Step 2								
Neutral Cond	.59**	.45**	.40**	--	.36**	.34**	.17	
ASPD Sx	.04	-.13	-.16	-.09	-.04	-.04	-.06	-.07
Familial Drug Use	-.03	-.01	.04	-.11	-.06	.01	.05	.08
Deviant Peers	.20*	.01	.08	-.11	.09	-.01	.05	.04
AUD Sx	-.10	.08	.01	.14	-.14	.20	.20	.02
Childhood Abuse	-.05	.15	.10	-.20	.06	-.15	-.24	.10
Childhood Neglect	.08	-.12	-.16	.18	-.09	.15	.12	.04
Money Ratings	--	--	--	--	--	--	--	-.21
Alcohol Task Order	--	--	--	.25*	--	--	--	--

Age Alcohol	-.05	.19*	.24*	-.28*	.09	-.02	-.01	.04
R-Squared Change	.00	.04*	.04*	.05*	.00	.00	.01	.00

Note. *p <.05; ** p <.01. ASPD Sx = Square-root transformed Antisocial Personality Disorder Symptoms from MINI; Neutral Cond = Neutral comparison wave to the cue or feedback; AUD Sx = Alcohol Use Disorder symptoms from MINI; Age Alcohol = Age of Alcohol Initiation. Step 1 includes our environmental and genetic covariates. Step 2 includes our main variable of interest, age of alcohol initiation.

APPENDIX E:

Scatterplots of Significant Results

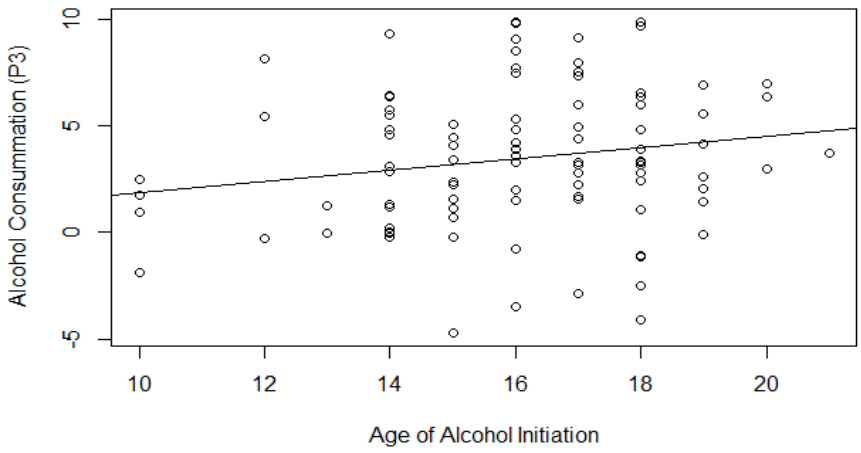

Figure E1. The Effect of Age of Alcohol Initiation on Alcohol Feedback-P3

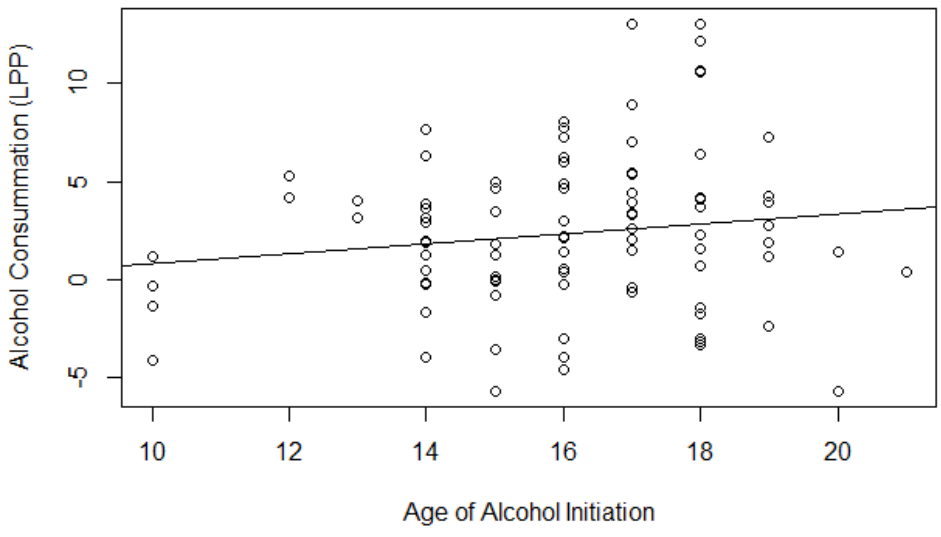

Figure E2. The Effect of Age of Alcohol Initiation on Alcohol Feedback-LPP