A Review of Developmental Considerations in Human Laboratory Alcohol Research

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Abstract

PURPOSE OF REVIEW—Human laboratory studies involving alcohol administration have generated critical knowledge about individual differences in risk for alcohol use disorder (AUD), but have primarily involved adult populations and cross-sectional research designs. Ethical constraints have largely precluded human laboratory alcohol research in adolescence, and prospective studies have been rare. This paper provides an overview of developmental considerations in human laboratory alcohol research, with a focus on studies conducted with youth.

RECENT FINDINGS—Recent human laboratory studies from Europe and Canada have examined aspects of alcohol response during late adolescence, while recent survey studies from the United States have highlighted methods for circumventing alcohol administration in studies of adolescents.

SUMMARY—Across several decades of research, exceedingly few laboratory studies have examined developmental differences in alcohol responses or utilized prospective designs. Efforts to prioritize prospective research would further clarify the role of alcohol sensitivity traits as predictors or markers of AUD onset and progression.

Keywords

addiction; adolescent; cue; craving; development; ecological momentary assessment; subjective response; review; youth

Introduction

Clinical research on alcohol use disorders (AUD) has historically relied on human laboratory methods to investigate aspects of AUD etiology and phenomenology. Representing an offshoot of the broader experimental psychopathology literature [1], human laboratory alcohol research has proven influential for characterizing behavioral, biological and psychopharmacological markers of AUD and evaluating candidate treatments [2, 3]. A recent review of this literature identified nine predominant laboratory paradigms - captured largely under the categories of *alcohol administration*, *alcohol self-administration*, and *cue exposure* - emphasizing acute alcohol administration and cue-induced craving procedures as key methodological tools [1].

Human laboratory research is guided in large part by the notion that between-person variation in responses to acute alcohol (or alcohol cues) might index liability for heavy drinking or AUD. This idea has received broad support, particularly from research on subjective responses to alcohol (i.e., reported psychopharmacological effects during intoxication; for review see [4, 5, 2, 6, 7]). Subjective responses are considered candidate endophenotypes (i.e., biologically based traits that index genetic predisposition for AUD [7, 8]), also representing candidate markers of AUD progression and treatment response under a Research Domain Criteria (RDoC) framework [9]. Psychometric analyses of alcohol challenge data have identified four primary domains of subjective responses: stimulation/hedonic effects, sedation/aversive effects, negative affect reduction, and craving/wanting [10, 11]. A key finding is that laboratory measures of subjective response predict future consumption and AUD symptoms in adult heavy drinkers [4, 12]. While representing just one class of alcohol response traits studied within a larger human laboratory literature [13], subjective responses have remained a focal point - likely reflecting the conceptual and methodological accessibility of these constructs - and will serve as a primary basis for this review.

A critical gap in the human laboratory alcohol literature is that these studies have, with few exceptions, focused on adult populations and cross-sectional research designs. The consequent shortfall of developmentally informative studies (e.g., those involving prospective analyses, adolescent populations, and/or comparisons across developmental stages) is noteworthy for at least three reasons. First, preclinical and human data show marked differences in alcohol consumption in adolescence compared to adulthood, perhaps partly attributable to developmental differences in alcohol sensitivity. Second, the prevailing neurobiological and cognitive theories of addiction are essentially neurodevelopmental theories, predicting changes in drug response over the transition from initial use to addiction. Therefore, a lack of developmentally informative studies limits the ability to test theoretical predictions about changes in alcohol responses as related to AUD onset and course. Third, historical alcohol exposure reflects a universal confound for laboratory studies of alcohol response, complicating inferences that differences in subjective responses across risk groups reflect differences in innate risk. This confound can potentially be reduced (though not eliminated) by studying relatively younger samples.

Based on these considerations, this paper aims to provide a brief and accessible review of developmental issues in human laboratory alcohol research, with a particular focus on studies with youth. After summarizing ethical considerations in alcohol administration research with youth, we outline the rationale for developmentally informative human laboratory studies, and briefly review recent findings from alcohol administration studies in samples ≥ 21 years old. We also describe select survey-based studies examining alcohol response traits in youth, as well as select laboratory studies that have examined developmentally informative questions in adulthood. As a point of comparison throughout, we reference preclinical (rodent) findings on alcohol response traits. Last, we note the need for prospective studies situated in a developmental psychopathology framework.

Human Laboratory Alcohol Research in Youth

History and Ethical Considerations—Alcohol administration studies involving children are exceptionally rare, but not unprecedented. In perhaps the only study conducted with children, researchers administered ethanol (.5ml/kg) to 22 participants with or without a family history of AUD; these participants averaged around 12 years of age [14]. Results suggested no group differences on measures of cognitive performance, mood, body sway, or hormonal measures during 4 hours post-consumption. In fact, the primary observation was a general lack of observable behavioral changes or apparent intoxication during what was believed to be participants' first experience with a moderate dose of alcohol. Since this report no similar studies have been published, and the majority of alcohol administration studies have been conducted with participants in adulthood, leading to a disparity between the preclinical and human literatures with respect to the developmental timing of studies on alcohol response traits (as depicted in Figure 1).

Not surprisingly, ethical and legal constraints largely account for the dearth of human laboratory alcohol research in youth. Alcohol administration studies with drinkers under age 21 are typically not possible in the United States (rarely, some U.S. groups have studied drinkers under age 21, perhaps reflecting regional or institutional variability in legal statutes or risk tolerance). Most studies with participants under 21 have been conducted outside the U.S., but these studies rarely include participants younger than late adolescence (for recent examples, see Table 1). Beyond any legal constraints, alcohol administration studies with youth require careful consideration of ethical issues. Published ethical guidelines for human alcohol administration include a focus on developmental issues, a primary consideration being that alcohol-naïve youth should not be involved in alcohol administration studies [15]. A particularly important ethical consideration relates to exposing the adolescent brain to alcohol. An extensive preclinical literature attests to the adverse neural and behavioral sequelae of adolescent alcohol exposure [16], including disruptions in neurogenesis, increased cell death, altered electrophysiology of hippocampal neurons, epigenetic changes, alterations in neurotransmitter systems, impaired cognitive function, and increased depressive- and anxiety-like symptoms in adulthood [17, 18, 16, 19–21]. Thus, potential risks of exposing the developing brain to acute alcohol clearly warrant careful attention. Estimating these risks is challenging, however, because minimum alcohol exposure thresholds for conferring long-term risks in humans have not been determined. For instance, among adolescents engaged in regular heavy drinking, it is unclear whether a single

laboratory exposure (or limited series of exposures) would confer incremental risks. Ethical guidelines state that such potential risks should be weighed against potentially important public health benefits of improving scientific understanding of adolescent drinking, concluding that the risk/benefit ratio of this research may in some cases be favorable [15].

The Rationale for Developmentally Informative Research Designs—Several factors argue for greater efforts to study alcohol response traits in developmentally informative human laboratory designs, particularly during the transition from adolescence to adulthood. First, both preclinical [22–24] and human epidemiological [25, 26] data show clear developmental differences in alcohol consumption, with adolescents often showing per-episode consumption rates 2–3x higher than those of adults [27]. These differences coincide with the finding that AUD onset peaks between 18–20 years [28, 29], with rates of alcohol-attributable harms, disease burden, and mortality also peaking in the developmental window spanning late adolescence to early adulthood [30, 31]. Importantly, preclinical findings further suggest clear developmental differences in sensitivity to the acute and post-consumptive effects of alcohol. Relative to adults, adolescent animals appear less sensitive to aversive alcohol effects (i.e., motor impairment, ataxia, sedative, and socially impairing effects) that might serve to limit intake, yet more sensitive to rewarding, locomotor/stimulant, and social-facilitating effects [32, 33, 24, 34]. These findings, presumably reflecting ontogenetic differences in brain maturation, raise important implications for understanding alcohol consumption in human adolescence, specifically by implicating differences in alcohol sensitivity traits as potential contributors to increased consumption and alcohol-related harms [34]. It follows that examining developmental aspects of alcohol responses in human adolescence is an important priority [35]. However, exceedingly few human laboratory studies [36, 37] have compared acute alcohol responses across developmental stages, and virtually no data exist on the association of laboratory measures of alcohol response with drinking trajectories over the transition from adolescence to adulthood.

Second, developmental human laboratory investigations can potentially help to validate theories of AUD etiology. Prevailing neurobiological theories of addiction (e.g., [38–41]) are fundamentally developmental in nature, emphasizing neuroadaptations that lead to altered hedonic, motivational and behavioral responses to drugs over the transition from casual to compulsive use. Generally, such theories also predict a shift in the balance between neural systems regulating impulsive/compulsive versus executive/controlled aspects of cognition and behavior, as well as a dissociation between drug “liking” and “wanting” as addiction progresses. Importantly, human laboratory studies can be leveraged to evaluate these predictions. In a test of Koob’s allostatic model [42], alcohol-dependent (AD) participants showed blunted sedation and craving responses across rising blood alcohol concentration (BAC) relative to heavy drinkers (HD), and the relation of subjective stimulation with craving was significantly weaker for AD vs. HD groups. A second, larger study showed a dose-dependent association of alcohol-induced stimulation with craving in HD, but not AD participants [43], suggesting a diminished functional association between stimulation and craving in AD participants (consistent with theories based on preclinical data).

Longitudinal studies involving laboratory components are necessary to test these predictions with greater specificity; however, these studies are exceedingly rare. Schuckit and colleagues' landmark San Diego Prospective Study served as the first example of a project integrating human laboratory and prospective cohort designs [44]. More recently, important findings from King and colleagues' Chicago Social Drinking Project showed that both hedonic and sedative responses during alcohol challenge predicted frequency of heavy drinking over a multi-year follow-up period [5], with subjective responses also predicting extent of AUD symptoms over a 6-year follow-up [12]. Of note, these prospective associations were limited to heavy drinkers, and were largely specific to subjective responses at a moderately high alcohol dose (.8g/kg). Critically, this study provided a prospective test of changes in laboratory responses over a 5-year period (participants averaged roughly 30 years of age at follow-up). Over this period the persistence of pronounced stimulant effects related to increasing AUD symptoms, whereas other predictions based on preclinical theories were not supported [45]. The significant time lag between the San Diego and Chicago projects illustrates the shortage of prospective human laboratory research [5].

Developmentally informative studies of alcohol response traits could also help to address inferential limitations of research on subjective responses. In conceptualizing drug responses as endophenotypic traits, many studies have interpreted group differences (e.g., heavy vs. light drinker status; positive vs. negative family history of AUD) as reflecting innate differences in alcohol response [2]. However, cross-sectional studies with adults cannot account for differences in historical alcohol exposure as partly contributing to results. Additionally, recruiting participants based on drinking patterns complicates inferences as to whether laboratory alcohol responses reflect innate or acquired differences. Finally, to the extent that clinically relevant changes in alcohol response traits precede AUD onset, findings from adult samples – typically recruited beyond the peak age of AUD onset – can be difficult to interpret. Most laboratory studies also exclude those with AUD, precluding those with more severe manifestations (e.g., early-onset AUD) from study. These considerations suggest that greater efforts are needed to study developmental aspects of alcohol responses, particularly over the period when at-risk drinking and AUD symptoms emerge.

Examples of Neurodevelopmental Changes in Alcohol Response: Tolerance and Sensitization—Examples of key neurodevelopmental aspects of alcohol response include tolerance and sensitization. Tolerance, the tendency for diminished subjective or behavioral effects of alcohol over time, can occur within a single alcohol exposure (acute tolerance), or following repeated alcohol exposures (chronic tolerance). Chronic tolerance to the aversive/impairing effects of alcohol (effects which would typically serve as cues to limit intake) is a risk factor for hazardous drinking [46], while acute tolerance to subjective effects can also place drinkers at situational risk for alcohol-related harms [47]. In the preclinical literature chronic tolerance is most often observed for sedative, ataxic, and social-impairing effects of alcohol, with adolescents demonstrating enhanced acute tolerance to these effects; in contrast, findings on age differences in chronic alcohol tolerance are mixed [48].

Sensitization refers to a more pronounced response to alcohol's effects over time. Sensitization to hedonic effects, often inferred based on exaggerated psychomotor responses

to alcohol, is a presumed index of neural changes induced by repeated alcohol exposure [49, 50]. Sensitization is thought to reflect acquisition of incentive salience for alcohol and associated cues [41]. In preclinical studies adolescents appear more sensitive to some rewarding properties of alcohol than adults, although the effect of age on locomotor sensitization has been inconsistent [32, 51, 52]. Tolerance and sensitization can occur simultaneously within different domains of alcohol response alcohol, presumably through independent neural mechanisms [53, 54]. Given the centrality of tolerance and sensitization to theories of addiction etiology [46, 41], the paucity of human developmental research on these fundamental processes - and their relation to AUD onset - is striking. To summarize, developmentally informed studies of alcohol response traits could help to evaluate age-related differences in these traits (and implications for consumption), evaluate the translational value of preclinical theories, overcome inferential difficulties in conceptualizing subjective responses as innate markers of AUD liability, and better characterize neurodevelopmental processes like tolerance and sensitization. Given substantial increases in alcohol consumption and related harms during the transition from adolescence to adulthood, this developmental period is opportune for studying these phenomena.

Recent Findings from Alcohol Administration Studies in Youth—Though most alcohol administration studies involve drinkers over age 21, several groups have included relatively younger samples, with most of this research occurring outside of the U.S. A representative list of recent (2013–2017) alcohol administration studies reporting a mean sample age ≥ 21 years, as identified by targeted literature searches, is presented in Table 1, and select findings and methods from these studies are reviewed below. Of note, age ranges for these studies are not markedly below the common cutoff of 21 years, and these studies largely did not investigate developmental questions. Nonetheless, given preclinical evidence for developmental changes in alcohol responses *within* adolescence [55], conducting human laboratory work within discrete age “bands” that fall between adolescence to adulthood, as reported in some of these studies, could ultimately be informative for understanding developmental differences in alcohol response traits.

Surprisingly, what appears to be the first alcohol administration study comparing adolescents to adults was published only recently [37]. In this study from Germany, adolescent and adult groups (averaging 16–17 years old and 41–42 years old, respectively) consumed alcohol or placebo before completing a battery of cognitive tasks. Despite some evidence of age differences in alcohol-related impairment on a measure of cognitive flexibility, the general lack of alcohol effects on cognitive performance precluded clear interpretations. Additional studies have investigated cognitive processes as related to acute alcohol intoxication, cue exposure, or other contextual influences [56–62]. Among these, several studies from the United Kingdom (U.K.) have used *ad libitum* alcohol consumption methods to study cognitive, contextual and intervention effects on objective measures of consumption [57] [58] [59] [61] [63]. In one study, inhibitory control training (using a modified Stop Signal task) led to decreases in laboratory consumption in young participants [59]. In another, two types of training - inhibitory control training and cue avoidance training - resulted in significant, comparable decreases in laboratory consumption [58]. Recent studies with youth

have also examined genetic associations with behavioral, subjective and neural markers of alcohol reward [64, 65], acute alcohol effects on food consumption [56] [66], and effects of alcohol on hypothalamic–pituitary–adrenal (HPA) activity [67] (see Table 1 for a summary of results).

A relatively recent development is the application of intravenous (IV) alcohol administration methods [68, 69] to study alcohol response traits in youth. Recent studies in Germany and Canada have used two paradigms: the *alcohol clamp* (which enables precise control over BAC profiles, including the ability to maintain pseudo-constant BAC for extended periods) and *intravenous alcohol self-administration (IVASA)* (in which participants can self-administer alcohol intravenously under free-access or operant schedules). Two studies used the alcohol clamp to examine cognitive and subjective responses to alcohol at an exposure level of 80mg%. In one [70], alcohol increased self-reported motivation to drink, but did not affect approach tendencies for alcohol cues (on an Approach Avoidance Task), and reduced preference for alcohol-related stimuli (as measured by a Pavlovian conditioning task). Another study [71] found that participants' reports of subjective stimulation and craving declined while BAC was held constant, while errors on a cognitive response inhibition task continued to increase; the latter effect was moderated by self-reported attention deficit symptoms and sensation seeking. Alcohol clamp methods are particularly valuable for functional imaging studies, which involve extended assessment intervals. Two studies examined alcohol's effects on neural markers of inhibitory control in youth [72, 73], while another two studies demonstrated BAC-dependent increases in regional cerebral blood flow, a finding that raises methodological implications for pharmacological fMRI studies [74, 75].

In recent IVASA studies with youth, adolescent women induced lower BAC levels and reported greater sedative effects relative to their male counterparts [76], and the extent to which alcohol impaired inhibitory control during an initial alcohol clamp session predicted adolescents' subsequent IVASA behavior [72]. Additionally, a short-term prospective study in late adolescence found that subjective stimulation and sedation during an alcohol clamp session predicted the extent of IVASA in a subsequent session [77]. In this study, peak BAC in the IVASA session predicted self-reported heavy drinking several months later, with self-administration accounting for indirect associations between background risk factors and future heavy drinking [77]. Moreover, the application of advanced statistical modeling to IVASA data showed that within-person fluctuations in subjective stimulation and sedation predicted event-level changes in IVASA behavior, with these associations being partly mediated by changes in craving [78]. Importantly, these recent studies illustrate that IVASA can be conducted safely with youth, with no evidence that participation in these studies is followed by increases in drinking [77, 79].

Alternative Approaches for Studying Alcohol Response Traits in Youth—Given the challenges associated with alcohol administration in youth, devising options for circumventing ethical barriers to laboratory alcohol administration is an important objective. At least four approaches have been utilized in studies of adolescents. First, questionnaire-based measures of alcohol sensitivity can serve as potential proxies for responses to acute alcohol. For example, the Self-Rating of the Effects of alcohol (SRE) questionnaire has been used in studies of children and adolescents [80, 81]. Researchers have also used the SRE to

estimate acquired tolerance by calculating differences between historical and current self-reported levels of response to alcohol [82]. These approaches are advantageous when laboratory alcohol administration is impractical, but the likelihood of measurement error and/or bias in recalling remote drinking events (e.g., one's first five drinking occasions) is a limitation. Other instruments assessing anticipated stimulant and sedative effects of alcohol [83, 84] could similarly be used in studies with youth.

An alternative approach involves remote, real-time assessment of adolescents' responses to alcohol using ecological momentary assessment (EMA). EMA relies on completion of self-report questionnaires at scheduled or random prompts, or during event-specific occasions (e.g., drinking episodes). The first EMA study to compare alcohol responses among adolescents versus adults found evidence for age-specific patterns in subjective responses [85]. Compared to adults, adolescents (ages 15–19 years; mean 18.3 years) reported greater mean stimulation, particularly at the beginning of drinking episodes, but showed significant declines in stimulation as estimated BAC (eBAC) increased—a pattern absent among adults. Moreover, craving (but not stimulation or sedation) predicted event-level consumption in adolescents, and a significant correlation of stimulation with craving was limited to adolescents [85].

A third method for circumventing alcohol administration is laboratory-based alcohol cue exposure. For example, in a rare adolescent alcohol pharmacotherapy trial, naltrexone attenuated baseline craving in the laboratory and cue-associated craving in the environment [86]. EMA assessments further showed that naltrexone reduced the likelihood of heavy drinking and influenced subjective responses during adolescents' drinking episodes [86]. Supporting the validity of cue-invoked craving methods with adolescents, alcohol cues elicited craving both in the lab and the natural environment, with responses to laboratory cues predicting the intensity of naturalistic craving [87].

A fourth approach involves direct ecological assessment of alcohol responses in naturalistic settings. For example, researchers recruited a large sample of participants (ages 17–32 years) from a bar district and collected data on subjective responses [88]. Self-reports of alcohol-induced stimulation were higher in younger compared to older participants, with these differences being more pronounced at lower BACs and among heavier drinkers [88]. Using a similar ecological recruitment approach, researchers found that acute intoxication related to executive functioning deficits in a group of 18–20 year-olds [89]. Overall, these findings highlight the utility of laboratory cue exposure and ecological measurements, including EMA, as complements to laboratory alcohol administration. Systematic use of these methods to study in-the-moment associations of subjective effects/craving with consumption, as well as age and contextual moderators, can further inform how acute subjective responses relate to risk for heavy drinking at different developmental stages. The increasing sophistication of passive alcohol biosensors and smartphone-compatible breath alcohol devices [90] will undoubtedly facilitate additional ecological research on adolescent alcohol responses in the near future.

Caveats and Limitations

Several caveats to this review should be considered. While we have reviewed basic considerations that argue for developmentally informative laboratory alcohol research, the measurement and interpretation of developmental changes in drug responses is a complex research endeavor, and the present discussion is not exhaustive. Similarly, our literature review aimed to summarize representative studies, but is not proposed as exhaustive. While we focused on alcohol responses in youth, it is important to note that adults of middle age and older are also neglected in this domain of research (Figure 1). Finally, while we offered some comparisons between human and preclinical studies to emphasize differences between literatures (and translational implications), direct or conclusive comparisons between preclinical and human studies are not possible, and achieving full consilience across these fields is not possible [27]. Importantly, many preclinical studies have used alcohol exposure levels that are not permissible in human laboratory studies, reporting BAC ranges up to or exceeding .20g%, and the outcomes commonly emphasized in preclinical studies (e.g., self-administration) have been under-emphasized in human studies [77, 69]. Conversely, while subjective responses serve as the most common outcome in human laboratory studies, there is no direct analogue of subjective responses in animal studies (for review see [91]).

Conclusion

Human laboratory investigations have proven critical for characterizing etiological aspects of AUD. As argued in this review and elsewhere, such studies have the potential to shed light on neurodevelopmental processes relevant for AUD onset and clinical course [43, 9, 7]. From this standpoint, the relative absence of studies examining developmentally informative questions reflects a significant knowledge gap. Across several decades of work, exceedingly few human alcohol administration projects have incorporated prospective components (e.g., [77, 4, 44]), addressed age differences, or studied participants before late adolescence. Notably, we identified only two studies reporting the explicit aim of comparing age cohorts on laboratory alcohol responses [36, 37]. Not surprisingly, a major barrier concerns the relative inability to conduct alcohol administration research between early and late adolescence for ethical reasons [71, 2]. Although these constraints will continue to limit the ability to apply alcohol administration protocols across the full developmental range, options for partly circumnavigating these barriers exist, as reviewed above.

Greater efforts to situate future research in a *developmental psychopathology* framework [35] should help to strengthen the science base on developmental aspects of alcohol response traits and their relation to AUD. Developmental psychopathology approaches emphasize the longitudinal study of etiologic factors in a “multiple levels of analysis” framework, the strategic use of laboratory and psychophysiological methods to study traits or endophenotypes that anticipate onset of mental health disorders, and the prospective examination of person-environment and gene-environment interactions [92]. In addition to providing a developmentally informed framework for the study of drug response traits, this approach is highly compatible with the RDoC initiative, itself a promising framework for studying subjective responses and related constructs [9]. While developmental psychopathology methods have greatly informed AUD research generally [35], the

assessment of alcohol response traits in such studies, particularly in laboratory contexts, represents an important objective. Future efforts to characterize subjective responses and associated markers of alcohol response (e.g., tolerance, sensitization) in prospective studies would help to clarify their role in AUD etiology and course.

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Figure 1.

Preclinical and human alcohol administration studies by year and developmental stage. Data points represent publications identified in systematic reviews of the preclinical and human literatures on alcohol sensitivity [49, 91, 2, 6, 69, 13] and supplementary literature searches. Estimated age reflects the reported mean or median sample age (human studies), or the estimated human-equivalent age (rodent studies), calculated by converting from postnatal day using previously reported formulas [93, 94]. For publications that reported an explicit aim of comparing age groups, each age group is denoted separately (open symbols). This summary of studies is representative and not exhaustive.

Table 1

Recent (2013–2017) alcohol administration studies involving participants with mean age 21 years.

Study	Sample	Study Location	Design/Laboratory Paradigm	Alcohol Dose/Peak BAC	Primary Findings
Jones and Field, 2013 [59]	N=90 Mean age: 20.79 (age range: 18–30) Heavy social drinkers 54% F	UK	Participants completed a modified stop-signal task and a modified antisaccade task to train motor and oculomotor inhibition, respectively. The influence of these manipulations on alcohol consumption (250 ml beer, 5% alcohol volume) was evaluated.		Training motor inhibition in the presence of alcohol-related cues led to reduced alcohol consumption in the laboratory but not self-reported drinking. Training of oculomotor inhibition in the presence of alcohol-related cues had no influence on alcohol consumption.
Mick et al., 2013 [67]	N=63 Mean age: 20.06 (FH+), 20.13 (FH–) Healthy men	Germany	Effect of alcohol ingestion on secretion of cortisol and adrenocorticotrophin (ACTH) was examined. Participants consumed alcohol on the first test day and placebo on the second test day.	0.6 g/kg	In FH– individuals, alcohol attenuated the secretion of both hormones. Alcohol did not effect hormone secretion in FH+ individuals. In both groups, the ratio cortisol to ACTH secretion was moderately increased, indicative of increased adrenal sensitivity.
Christiansen et al., 2013 [57]	N=31 Mean age: 21.03 (age range: 18–40) Healthy social drinkers 61% F	UK	Participants consumed alcohol, a placebo, or a control beverage and then completed a test battery containing a measure of alcohol-approach tendencies, executive function, a taste test, and craving.	0.65 g/kg/0.96 g/100ml	Alcohol administration impaired executive function performance, increased <i>ad libitum</i> drinking, and increased craving. Alcohol approach tendencies were not different between alcohol and placebo conditions, although both were increased compared to the control beverage condition.
Scheel et al., 2013 [37]	N=44 (21 adolescents, 23 adults) Mean age: 16.80 (adolescent-alcohol), 16.55 (adolescent-placebo), 42.17 (adultalcohol), 41.36 (adultplacebo) 55% F	Germany	This study compared the effects of low dose alcohol on attentional performance in adolescents and adults. Participants received alcohol or placebo and completed the Test of Attentional Performance to assess alertness, working memory, flexibility, and divided attention before and after consuming their drink.	0.06% target (adolescent mean: 0.054%; adult mean: 0.055%)	Performance on the Flexibility subtest showed less improvement in the adolescent/alcohol group compared to the non-alcohol condition, and compared to adult groups. Alcohol impaired performance on the Working Memory subtest, but alcohol effects on cognitive performance were limited overall. Results suggest that adolescents might be vulnerable to alcohol's effects on cognitive flexibility.
Marxen et al., 2014 [74]	N=48 (age range: 18–19) Healthy young adults 35% F 27% FH+	Germany	Participants underwent arterial spin labeling (ASL) magnetic resonance imaging sessions, once under alcohol exposure (intravenous 6% solution) and once under a placebo (saline) condition to examine the effects of alcohol on brain perfusion. The intravenous alcohol session consisted of an ascending limb (0 to 15 min) and a BrAC plateau (15–130 min).	0.6 g/kg	Alcohol produced a 7 % increase in global perfusion, which was significant in most areas of the brain. This effect was more pronounced in women than in men. Alcohol-induced brain perfusion and BrAC were tightly coupled in time.
Rose et al., 2014 [62]	N=142 Mean age: 20.33 Healthy drinkers 53% F	UK	Participants completed a behavioral measure of risk taking (the Balloon Analogue Risk Task, BART) after consuming alcohol or placebo. Impulsivity and sensation-seeking were measured (Sensation Seeking Scale and Barratt's Impulsivity Scale)	0.6 g/kg 0.036 mg/l	Consumption of alcohol increased drinking urge and risk taking on the BART. In the alcohol group, risk taking on the BART predicted variance in weekly alcohol consumption and bingeing.

Study	Sample	Study Location	Design/Laboratory Paradigm	Alcohol Dose/Peak BAC	Primary Findings
Gan et al., 2014 [72]	N = 42 Mean age: 19.10 Social drinkers 26% F	Germany	Participants received alcohol or saline infusions while completing a stop signal task during functional imaging. Participants also completed two free-access intravenous alcohol self-administration sessions on separate days.	.6g/kg	Alcohol impaired inhibitory control. The extent of inhibitory control impairment was associated with reduced activation in the right inferior frontal gyrus/anterior insula and right middle occipitotemporal cortex. The extent of alcohol-induced impairment in inhibitory control also correlated with the number of alcohol requests in the second alcohol self-administration session.
Gan et al., 2015 [73]	N=35 Mean age: 19.10 Social drinkers 31% F	Germany	While receiving intravenous saline or alcohol, participants underwent an fMRI and performed a variant of the Taylor aggression paradigm (TAP) that distinguished between provoked and unprovoked aggression.	0.63–0.64 g/kg	Alcohol and provocation increased aggressive responding and decreased activity in the anterior cingulate cortex/dorsomedial prefrontal cortex. Greater alcohol-induced aggression was related to increased amygdala and ventral striatum reactivity under alcohol.
Rose et al., 2015 [66]	N=114 Mean age: 20.3 Social drinkers 58% F	UK	To investigate the effect of an alcohol priming dose and an alcohol-related environment on snacking behavior, participants received a priming dose of alcohol or soft-drink in a bar lab or sterile lab. Participants provided ratings of appetite, snack urge, and alcohol urge before and after consuming their drinks, and completed an ad libitum snack taste test.	0.6 g/kg	Appetite, snack urge, and total calories consumed increased following alcohol consumption. Those in the bar-lab environment consumed more unhealthy foods. These effects were more pronounced in disinhibited individuals.
Sommer et al., 2015 (Study 2) [78]	N=102 Mean age: 18.3 and 18.4 (control group) (age range: 18–19) Social drinkers 57% F	Germany	Participants completed two free-access intravenous self-administration sessions. Participants completed calendar-based assessments of drinking that spanned 6 weeks prior to and 6 weeks after the laboratory protocol.	Ceiling: 120mg%	Participants reported slightly less consumption following the alcohol self-administration sessions, indicating that laboratory alcohol self-administration sessions were not associated with subsequent increases in consumption.
Strang et al., 2015 [75]	N=20 Mean age: 19.95 (age range: 19–21) Heavy drinkers 45% F	Canada	Participants underwent fMRI sessions, once following intravenous alcohol and once following a saline control infusion. ASL provided estimates of alcohol-related changes in cerebral blood flow at two target BrACs (40 and 80 mg%) relative to baseline and saline. Self-reported alcohol sensitivity was measured (SRE).	81 mg%	Alcohol increased cerebral blood flow in a dose-dependent manner, with regional variation in the magnitude of the perfusion change. Lower self-reported sensitivity to alcohol corresponded with reduced perfusion change in some regions during alcohol administration.
Hendershot et al., 2015 [71]	N = 88 Mean age 19.81 (F) and 19.71 (M) (age range: 19–21) Young heavy drinkers 52% F	Canada	Participants completed an intravenous alcohol session consisting of an ascending limb (0 to 20 min) and a BrAC plateau (20–100 min). Inhibitory control and subjective responses were serially measured with a cued go/no-go task and measures of stimulation and sedation (BAES), and craving (AUQ). ADHD symptoms (ASRS) and sensation seeking were examined as moderators.	80mg%	Response inhibition worsened following initial rise in BrAC and showed increasing impairment during the BrAC plateau, with ADHD symptoms and sensation seeking moderating this effect. Those with higher ADHD symptoms reported steeper increases in stimulation during the ascending limb. Within-subject associations between stimulation and craving were evident during the ascending limb.
Wardell et al., 2015 [78]	N=62 Mean age: 19.90 (age range: 19–21)	Canada	Participants completed a 2 hr intravenous alcohol self-administration session. Repeated assessments (BAES, craving) were taken across the session and	Ceiling: 100mg% Mean Peak: 82.08 mg%	At the between-person level, there was a negative association between sedation and BrAC. At the within-person level, state

Study	Sample	Study Location	Design/Laboratory Paradigm	Alcohol Dose/Peak BrAC	Primary Findings
Christiansen et al., 2016b [56]	Heavy drinkers 52% F N=60 Mean age: 19.64 Healthy social-drinking females	UK	examined as predictors of subsequent increases/decreases in BrAC. Self-reported impaired control and impulsivity (ICS, ImpSS) were examined as additional predictors.	0.6g/kg	fluctuations in stimulation were positively associated with craving and subsequent BrAC, whereas state fluctuations in sedation were negatively associated with craving and positively associated with BrAC. Participants with higher impaired control showed stronger within-person associations between craving and greater subsequent BrAC. Alcohol impaired inhibitory control and increased calories consumed; inhibitory control impairments mediated the effect of alcohol on consumption. The mediation effect was evident at low/moderate, but not high levels of self-reported dietary restraint.
Hendershot et al., 2016a [64]	N = 40 45% F Young heavy drinkers Stratified by <i>OPRM1</i> genotype (rs1799971) Mean age 19.93 (AA) and 20.00 (GA/GG) (age range: 19–21) Young heavy drinkers	Canada	Participants completed a 2 hr computer-assisted self-infusion of ethanol (CASE) session consisting of a priming phase followed by ad libitum self-administration in a free-access paradigm. Subjective measures included the AUQ, DEQ, and BAES	Ceiling: 100mg% GA/GG genotypes: 94.90mg% AA genotypes: 74.46mg%	Individuals with the GA/GG genotype achieved significantly higher peak BrACs than AA individuals, reflective of greater alcohol requests in this group. Eighty-percent of GA/GG participants surpassed a lab analog of heavy alcohol exposure compared with 46% of AA participants. Subjective responses did not differ by <i>OPRM1</i> status, although there were significant associations between measures of alcohol response and self-administration.
Hendershot et al., 2016b [77]	N = 61 52% F Young heavy drinkers Stratified by FH+/FH- and <i>OPRM1</i> genotype (rs1799971) Mean age 19.82 (FH-), 19.96 (FH+), 19.91 (AA), and 19.81 (GA/GG) and 20.00 (age range: 19–21)	Canada	Participants completed two intravenous alcohol laboratory sessions. The first was an alcohol clamp challenge and the second was a free-access self-administration session. Laboratory phenotypes were assessed in relation to genetic risk factors (family history [FH] and <i>OPRM1</i> genotype), and subjective responses (measured using BAES). Laboratory measures were examined as predictors of self-reported heavy drinking 6 months later.	Session 1 clamp: FH-: 80.41mg% FH+: 80.05mg% AA: 80.24mg% GA/GG: 80.26mg% Session 2 free-access: FH-: 80.94mg% FH+: 84.52mg% AA: 78.51mg% GA/GG: 93.81mg%	Higher reported stimulation and sedation in Session 1 predicted greater alcohol self-administration during Session 2. Self-administration did not differ by FH group, however GA/GG individuals demonstrated greater peak BrAC compared to AA individuals. Peak stimulation and sedation in Session 1 independently predicted self-administration in Session 2. Results supported significant indirect associations between Session 1 subjective responses and 6-month heavy drinking, mediated via Session 2 BrAC, as well as significant (indirect) associations of FH and <i>OPRM1</i> genotype with follow-up heavy drinking, mediated via Session 2 BrAC.
Jünger et al., 2016 [76]	N = 82 Mean age 18.5 (M, FH+), 18.4 (M, FH-), 18.3 (F, FH+), and 18.4 (F, FH-) (age range: 18–19) 43% F 46% FH	Germany	Associations of sex and family history with laboratory alcohol self-administration were examined using a free-access intravenous (IV) alcohol self-administration paradigm. Subjective measures were also assessed using the AEQ.	Ceiling: 120mg% FH- (M): mean BrAC approx. 63mg% FH+ (M): mean BrAC approx. 61mg%	Greater self-reported drinking was associated with higher mean BrACs in the laboratory. Women reported less drinking than men and achieved a lower mean BrAC in the laboratory. Women reported greater sedation relative to men. Being FH+ was associated with lower real-life drinking in men, but not women. In the laboratory, FH

Study	Sample	Study Location	Design/Laboratory Paradigm	Alcohol Dose/Peak BAC	Primary Findings
Korucuoglu et. al., 2016a [65]	N = 36 Stratified by <i>OPRM1</i> genotype (rs1799971) Mean age 19.2 (AA) and 18.21 (AG) (range: 17–21) 64% F	Netherlands	Participants underwent an alcohol versus water taste-cue reactivity paradigm while undergoing an fMRI. Before and after the scanning session, participants received a sample of the experimental taste stimuli [alcohol (1ml of 6.4% vol.) and water] and rated the pleasantness on a 10-point scale.	FH+ (F): mean BrAC approx. 45mg% FH– (F): mean BrAC approx. 38mg%	was not associated with alcohol requests during the IV session.
Korucuoglu et. al., 2016b [60]	N = 33 Mean age 18 (LD) and 17.4 (HD) (age range: 16–20) 61 % F	Netherlands	Alcohol-induced changes on approach-avoidance responses and EEG asymmetries were compared in LD and HD. Participants completed an alcohol approach-avoidance task (AAAO) after consuming alcohol or a placebo. Subjective measures included the B-BAES, DAQ, and the PANAS. Drinking restraint was measured using the TRI.	0.45 g/kg Mean value (prior to completing the alcohol-approach-avoidance task): 0.55g/L	The AG group showed reduced activation in prefrontal and parietal regions compared to the AA group. Connectivity from the ventral-striatum to frontal regions for alcohol trials were higher in the AG than the AA group. The AG group also showed increased connectivity from the dorsal striatum seed region to non-PFC regions. Following alcohol, a non-significant decrease for approach alcohol bias was observed. This effect was larger in the HD group. A strong approach soft drink and weak approach alcohol reaction-time bias after alcohol predicted decreased follow-up drinking. In HD, increased approach-related asymmetry in the beta-band was seen for soft-drink cues compared to alcohol cues and this was associated with increased difficulty in regulating alcohol intake.
McGrath et. al., 2016 [61]	N=100 Mean age: 20.86 Heavy drinkers 52%F	UK	Heavy drinkers were randomized to receive a stress induction or no induction, completing a stop signal task before and after the induction. Participants then conducted a bogus taste test to measure alcohol self-administration.		Acute stress resulted in increased ad libitum alcohol consumption, but did not influence inhibitory control.
Robinson et. al., 2016 (Study 1) [63]	N=80 Mean age: 19.2 Social drinkers 73%F	UK	Participants' ad libitum alcohol consumption during a social encounter was assessed as a function of two experimental manipulations: confederate drinking level and heightened ingratiation motives.		Participants were more likely to mimic drinking of a confederate if they perceived subsequent judgment (high ingratiation condition).
Di Lemna and Field, 2017 [58]	N=120 Mean age: 20.37 (age range: 18–25) Heavy drinkers 72% F	UK	Heavy drinkers received active or control versions of two cognitive training interventions (inhibitory control training, cue avoidance training), and later completed a bogus taste test to measure ad libitum alcohol consumption.		Both interventions led to significant reductions in ad libitum consumption, although there was no difference between the two, and neither task appeared to influence alcohol-related implicit cognitions.
Jünger et. al., 2017 [70]	N= 51 males (age range: 18–19) Healthy social drinkers	Germany	Participants received an intravenous infusion of alcohol or saline. Implicit (Pavlovian Conditioning and Approach-Avoidance Task) and explicit (self-rating measures) motivation were administered.	80 mg%	Alcohol administration increased explicit (self-report) motivation to drink alcohol, whereas the opposite effect was observed with regarding implicit motivation. Explicit and implicit measures of motivation were not associated with each other, but correlated with self-reported drinking problems.

AAAQ=Approach and Avoidance of Alcohol Questionnaire
 AEQ= Alcohol Expectancy Questionnaire
 ASQ= Alcohol Sensitivity Questionnaire
 ASRS= World Health Organization Adult ADHD Self-Report Scale
 AUQ = Alcohol Urge Questionnaire
 BAES = Biphasic Alcohol Effects Scale
 B-BAES= Brief Biphasic Alcohol Effects Scale
 BrAC = Breath Alcohol Concentration
 DAQ= Desire for Alcohol Questionnaire
 DEQ = Drug Effects Questionnaire
 EEG= Electroencephalogram
 F = Female
 FH+ = Family History of Alcohol Dependence
 FH- = No Family History of Alcohol Dependence
 fMRI= Functional Magnetic Resonance Imaging
 HD=Heavy Drinkers
 ICS: Impaired Control Scale
 ImpSS=Impulsive Sensation Seeking Scale
 LD=Light Drinkers
 M = Male
 N = Number of participants
 PANAS = Positive and Negative Affect Schedule
 POMS= Profile of Mood States
 SEVAS=Subjective Effects Visual Analogue Scale
 SHAS = Subjective High Assessment Scale
 SRE= Self-Rating of the Effects of Alcohol Scale
 TRI= Temptation and Restraint Inventory
 UK = United Kingdom