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Subjective Response to Alcohol Challenge: A Quantitative Review

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Abstract

Background—Individual differences in subjective response to alcohol, as measured by laboratory-based alcohol challenge, have been identified as a candidate phenotypic risk factor for the development of alcohol use disorders (AUDs). Two models have been developed to explain the role of subjective response to alcohol, but predictions from the two models are contradictory, and theoretical consensus is lacking.

Methods—This investigation used a meta-analytic approach to review the accumulated evidence from alcohol-challenge studies of subjective response as a risk factor. Data from 32 independent samples (total $N = 1,314$) were aggregated to produce quantitative estimates of the effects of risk group status (i.e., positive family history of AUDs or heavier alcohol consumption) on subjective response.

Results—As predicted by the Low Level of Response Model (LLRM), family history positive groups experienced reduced overall subjective response relative to family history negative groups. This effect was most evident among men, with family history positive men responding more than half a standard deviation less than family history negative men. In contrast, consistent with the Differentiator Model (DM), heavier drinkers of both genders responded 0.4 standard deviations less on measures of sedation than did lighter drinkers but nearly half a standard deviation *more* on measures of stimulation, with the stimulation difference appearing most prominent on the ascending limb of the blood alcohol concentration curve.

Conclusions—The accumulated results from three decades of family history comparisons provide considerable support for the LLRM. In contrast, results from typical consumption comparisons were largely consistent with predictions of the DM. The LLRM and DM may describe two distinct sets of phenotypic risk, with importantly different etiologies and predictions for the development of AUDs.

Keywords

Subjective Response to Alcohol; Level of Response; Differentiator Model; Meta-Analysis

The study of twins has estimated that approximately 50% of the variance in alcohol use disorder (AUD) status is explained by genetic influences (Liu et al., 2004; Prescott and Kendler, 1999). The substantial heritability of AUDs has led to efforts to identify the genetic contributions to this major public health concern. Because AUD diagnosis reflects a clinical syndrome likely resulting from multiple distinct sets of risk factors (Hines et al., 2005), the specific factors, referred to as intermediate phenotypes, that reflect genetic influences on AUDs have been a major focus of research in recent years (Schuckit, 2009).

One potential intermediate phenotype is subjective response to alcohol. Schuckit (1980) first demonstrated that men with a positive family history of AUDs (FH+) responded less to the effects of alcohol relative to men with a negative family history (FH-) three decades ago. The etiological role of subjective response to alcohol continues, however, to be a source of both research and disagreement (for recent reviews and critiques, see Morean and Corbin, 2010 and Newlin and Renton, 2010). The Low Level of Response Model (LLRM), arguably the most widely accepted model of subjective response as a phenotypic risk factor, proposes that FH+ individuals experience lower subjective response to alcohol relative to FH- individuals (Schuckit, 2009). The model further suggests that “if individuals drink for effects and more alcohol is required to achieve the feelings they want, [low responders] are more likely to drink more heavily,” which leads to a greater likelihood of developing tolerance, withdrawal, and dependence (Schuckit, 2009, p. S7).

Evidence for the LLRM first came from alcohol-challenge studies, which compared responses to set doses of alcohol administered in controlled laboratory settings among FH+ and FH- men matched for typical alcohol consumption. The level of response has been measured with self-report questionnaires, notably including the Subjective High Assessment Scale (SHAS; Judd et al., 1977; Schuckit and Gold, 1988), but studies have also demonstrated a similar effect on physiological responses, including static ataxia (Schuckit, 1985), cortisol, prolactin, and adrenocorticotrophic hormone release (Schuckit et al., 1987a; Schuckit et al., 1987b; Schuckit et al., 1988b), and electroencephalographic background activity (Ehlers and Schuckit, 1991) and P300 event-related potential latency (Schuckit et al., 1988a). Recent research has also begun identifying neural correlates of level of response to alcohol (Trim et al., 2010). Additional support for the role of subjective response to alcohol as an intermediate phenotype comes from a study of twins, which estimated the heritability of level of response at approximately 60% (Heath et al., 1999), and from studies demonstrating specific molecular genetic associations with level of response (e.g., Corbin et al., 2006; Hinkers et al., 2006; Hu et al., 2005; Lind et al., 2008; Schuckit et al., 1999). Moreover, low response to alcohol predicts the development of AUDs in longitudinal studies (Schuckit, 1994; Schuckit and Smith, 1996; Schuckit and Smith, 2000; Schuckit and Smith, 2001; Schuckit et al., 2007; Trim et al., 2009). Consistent with its development as a model of risk among sons of alcoholics, the LLRM appears to apply more to men than to women. An early meta-analysis estimated that FH+ men responded approximately one third of a standard deviation less than did FH- men (Pollock, 1992), but several studies have failed to replicate the effect among women (e.g., Evans and Levin, 2003).

If the LLRM accurately explains the accumulated data derived from alcohol-challenge studies, it would be reasonable to conclude that a low level of response to alcohol is an inherited intermediate phenotype for the development of AUDs. Complicating this account, however, is the non-trivial number of studies failing to replicate the effect. In fact, in a number of alcohol challenges, those at risk have demonstrated *greater* response to alcohol (e.g., Earleywine, 1995; Lex et al., 1994; Moss et al., 1989). Whereas some authors have argued that these contradictory findings result from small sample sizes and differing alcohol-administration protocols (e.g., Hines et al., 2005; Schuckit et al., 2010), others have noted that much of the early evidence for the LLRM derived from comparisons made as BACs decline—the period during which alcohol tends to produce more aversive, sedative effects (e.g., Schuckit et al., 2005). As an alternative to the LLRM, Newlin and Thomson (1990) proposed that a Newtonian Differentiator Model (DM) might more accurately explain differences between FH+ and FH- groups. The DM states that those at risk for AUDs “may be more sensitive to the drug during the rising blood alcohol curve, when euphoria is greatest, and less sensitive during the falling curve, when anxiety and depression are greatest” (Newlin and Thomson, 1990, p. 399). That is, the DM proposes that a greater response to the positive, stimulant effects of alcohol, which are most prominent on the

ascending limb of the BAC curve, and a lower response to the aversive, sedative effects of alcohol, which are most prominent on the descending limb of the BAC curve, may serve as a risk factor for AUD. The DM therefore makes some similar predictions to those of the LLRM. It critically differs, however, in predicting greater response among those at risk under three conditions: on the ascending limb of the BAC curve, on measures of the positively reinforcing stimulant effects of alcohol, and, most specifically, on stimulant measures during the ascending limb.

An early meta-analysis of alcohol-challenge studies failed to find support for the DM (Pollock, 1992). That meta-analysis, however, preceded the development of self-report measures that explicitly capture the euphoric, stimulant effects of alcohol. Included studies used single-item measures of intoxication and the SHAS, which largely assesses the negative, sedative effects of alcohol (Ray et al., 2009). The DM account has benefitted from the validation and use of the Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993), an alcohol response questionnaire designed to assess both stimulant and sedative effects. More recent comparisons of FH+ and FH− participants using the BAES have found some support for the DM (e.g., Erblich et al., 2003). Additionally, although the DM was originally developed to explain FH differences, comparisons of heavier versus lighter drinkers have also produced results consistent with the DM (e.g., King et al., 2002; Marczinski et al., 2007). These studies of typical consumption are qualitatively distinct from FH comparisons, and they have differing and important limitations. Notably, they cannot establish that differences in subjective response precede patterns of alcohol use. Nonetheless, they can potentially provide evidence that greater response to the positively rewarding effects of alcohol is associated with risk for the development of AUDs.

The Current Investigation

The study of subjective alcohol response as an intermediate phenotype is entering its fourth decade, yet consensus regarding how best to understand this potentially important risk factor is still lacking. As a recent narrative summary of the area concluded, “although additional research may ultimately find that one of the two leading theoretical models is more accurate, the reviewed literature does not yet provide a definitive answer” (Morean and Corbin, 2010, p. 391). Indeed, despite presenting theories with contradictory predictions, prior reviews summarizing both the LLRM and the DM continue to be influential. According to the PsycInfo database, Pollock’s (1992) meta-analysis of evidence for the LLRM has been cited 77 times, including 6 citations in 2010 alone, and Newlin and Thomson’s (1990) presentation of the DM has been cited 147 times, including 14 citations in 2010.

In the present review, we used meta-analytic methods to quantitatively evaluate evidence from alcohol-challenge studies regarding differences in subjective response among low- and high-risk individuals. Whereas several narrative articles have periodically summarized this research area, it has been nearly two decades since Pollock’s (1992) meta-analysis. During that time, subjective response research has intensified, and several important advances—including the development of measures of subjective stimulant alcohol effects—have been made. Although narrative reviews have several important strengths, such as the inclusion of evidence from multiple methodologies, meta-analytic reviews have their own distinct and complimentary advantages. Meta-analysis provides more information, including explicit estimates of both effect size and heterogeneity, and the conclusions generated by meta-analyses are less biased relative to traditional, vote-counting approaches (Schmidt, 2010). Relevant to the current investigation, meta-analytic methods can permit an explicit test of the LLRM and DM given the accumulated evidence, and they additionally allow tests of whether third variables (e.g., gender) predict differences in the effect of at-risk status on subjective alcohol response.

This review aimed first to estimate the overall difference in subjective response to orally administered alcohol challenge between those at risk and those not at risk. Although subjective response has also been studied using retrospective surveys (e.g., Schuckit et al., 1997) and intravenous alcohol administrations (e.g., Ray et al., 2006), we limited our investigation to the oral challenge paradigm, which has been studied more and—relative to intravenous paradigms—more closely approximates real-world alcohol consumption. Because studies of subjective alcohol response have increasingly compared participants as a function of typical alcohol consumption rather than FH, we included studies from both methodologies but analyzed each separately. Second, given prior results suggesting that subjective response risk—particularly that conferred by FH—may be limited to men, we tested whether subjective response differences were moderated by gender. Finally, and most importantly, we quantitatively summarized the evidence from critical tests of the LLRM and DM. Predictions from the two models differ regarding the effect of risk status on subjective response on the ascending limb of the BAC curve and on measures of subjective stimulation. Estimates of the magnitude and direction of the risk-status effect in these cases provided the strongest evaluations of the two models.

Method

Sample of Studies

In February 2009 and then again in September 2010, we conducted a search of the PsycInfo database for articles examining subjective response to alcohol in lab-based challenge studies. Specifically, we searched for articles containing at least one of the following keywords: *subjective intoxication*, *level of response*, *subjective perception of intoxication*, *biphasic alcohol effects scale*, and *subjective high assessment scale*. Additionally, we searched for the following keywords in conjunction with *alcohol* or *ethanol*: *response*, *subjective effects*, *subjective response*, and *differentiator model*. These searches resulted in a total of 471 unique articles. We next searched the reference sections of prior review articles and critiques (Morean and Corbin, 2010; Newlin and Renton, 2010; Newlin and Thomson, 1990; Pollock, 1992) and the personal collection of the first author for potentially relevant articles not captured by the database searches. These search methods generated 44 unique articles. Finally, we searched the reference sections of relevant articles, generating 38 additional articles.

The three search methods yielded a total of 554 unique published articles,¹ the abstracts of which were screened for relevance (e.g., human subjects, alcohol-challenge design). Each of the 101 potentially relevant articles was obtained and coded by at least two trained, independent coders. Conflicts between coders were resolved by the coders and first author through consensus after additional examination of the articles. Coders examined each study using the following inclusion criteria: (a) the study described a lab-based alcohol-challenge study with human participants, (b) participants received a dose of alcohol which brought all participants to the same blood alcohol concentration (BAC), (c) participants consumed alcohol orally and were not maintained at a stable BAC (i.e., participants' BACs were allowed to descend naturally), (d) participants self-reported their subjective response to alcohol, and (e) risk for alcohol use disorders (AUDs) was assessed as a function of FH or typical alcohol consumption.

Of the 101 articles identified as potentially containing relevant studies, 41 did not meet the above inclusion criteria. Moreover, an additional 20 articles (33% of the eligible articles)

¹We did not include unpublished articles and dissertations because of concerns about study quality. Given the many catastrophic errors possible in the design, implementation, and analysis of alcohol-challenge studies (e.g., variability in alcohol dosage), we relied upon peer-reviewed publication as an index of internal validity.

were excluded because at least two coders determined that they contained samples that overlapped with those of included articles. Of the 40 eligible, unique articles, only 14 contained sufficient information in tables and text to generate effect sizes. We therefore attempted to contact authors of the remaining 26 articles, and we received data for an additional 7 articles via email. Of the 19 articles still lacking sufficient data, we were able to calculate effect sizes from means and standard errors estimated from figures for 8 articles.² The final sample comprised 29 published articles (73% of the eligible, non-duplicate articles) with $k = 32$ independent samples and $N = 1,314$ total participants. Of these samples, 19 ($n = 716$) tested differences in subjective response as a function of FH, and 13 ($n = 598$) tested differences as a function of typical alcohol consumption. See Tables 1 and 2 for included FH and typical consumption studies, respectively.

Coded Variables

Comparison type—FH comparisons tested differences between FH+ and FH− groups when matched on alcohol consumption. In most samples, FH+ was defined as having a biological father who met diagnostic criteria for an AUD, although the risk definition included paternal or maternal diagnosis in five studies and paternal, maternal, or sibling diagnosis in another five studies.

Typical drinking comparisons tested differences as a function of alcohol consumption. Eight such samples categorized participants into lighter and heavier drinking groups, with four of these contrasting non-binge-drinkers with those who weekly or “typically” reached the standard definition of binge drinking (i.e., four or more drinks in a sitting for women, five or more for men; Wechsler and Isaac, 1992). Two additional samples compared the 9 lightest drinking participants with the 9 heaviest drinking participants, 1 sample grouped participants on the basis of a median split on a measure of typical weekly consumption, and 1 compared participants who consumed fewer than 4 drinks per week with those who consumed 7–14 drinks per week. The five remaining samples examined the association between subjective response scores and continuous measures of alcohol consumption (i.e., frequency of alcohol consumption, quantity of alcohol consumed per occasion, and weekly alcohol consumption).

Subjective response measure—Assessment measures included validated self-report scales of subjective alcohol response such as the Subjective High Assessment Scale (SHAS; Judd et al., 1977; Schuckit and Gold, 1988), Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993), and Addiction Research Center Inventory (ARCI; Martin et al., 1971). They also included mood scales such as the Profile of Mood States (POMS; McNair et al., 1971), which have been commonly used to assess response to alcohol challenge. Finally, other studies assessed subjective response using single-item or multiple-item assessments of intoxication or impairment.

Subjective response measure type—When possible, we coded subjective response measures as assessing either stimulation or sedation. We based coding in part on a recent factor analytic study of measures of subjective alcohol response, which empirically differentiated measures of sedation from measures of stimulation (Ray et al., 2009). Sedation measures included the SHAS, BAES Sedation subscale, and ARCI Pentobarbital-Chlorpromazine-Alcohol Group subscale. Stimulation measures included the BAES Stimulation subscale, POMS Vigor subscale, and ARCI Amphetamine subscale. Eight samples (25% of the included samples) exclusively used measures that could not be coded as assessing either stimulation or sedation (e.g., *how impaired do you think you are at*

²Effect sizes estimated from figures did not differ from those obtained via other methods, $Q_{\text{between}}(1) = 2.04, p = .15$.

present?). These samples were therefore excluded from all analyses limited to stimulation or sedation.

Subjective response measure limb—We coded the time duration between alcohol administration and subjective response assessment. Using text descriptions and BAC curve figures, we then coded each assessment as having occurred on the ascending limb, at the peak, or on the descending limb of the BAC curve. We also recorded the peak BAC reached during the challenge.³ When studies included multiple assessments within a BAC limb, effect sizes were averaged across all assessments per limb.

Demographics—We coded studies on the basis of their gender distributions. Because the Low Level of Response Model (LLRM) and Differentiator Model (DM) were originally developed to explain differences in subjective response among FH+ and FH− men, we categorized samples as either *all male* or *not all male*. With the exception of one sample (mean age = 37.6 years), samples ranged in mean age from 20–30 years. We therefore did not test for differences in subjective response to alcohol as a function of age.

Effect Size Analyses

The difference between subjective response scores for at-risk and not-at-risk groups was the effect size of interest. Because they reflect different risk factors with potentially differing etiologies, we estimated effect sizes for the two comparison types (i.e., FH and typical consumption) separately. We computed Hedge's *g*, the bias-corrected standardized mean difference, using Comprehensive Meta-Analysis (Borenstein et al., 2005). Hedge's *g* is interpreted as the standardized mean difference and is more conservative than Cohen's *d* in small samples (Borenstein et al., 2009). Conventional benchmarks for small, medium, and large effects are $g = 0.2$, 0.5 , and 0.8 , respectively (Cohen, 1988). Where reported, means, standard deviations (or standard errors), and sample sizes for at-risk and not-at risk groups were used to calculate *g*. When these were not available, we estimated means and standard deviations using figures. When statistics for continuous variable associations were reported (e.g., for associations between subjective response and a measure of typical alcohol consumption), we recorded correlation coefficients and sample sizes. These were converted to Hedge's *g* in Comprehensive Meta-Analysis (Borenstein et al., 2005).

Of the 29 articles included in the meta-analysis, three presented results for more than one independent sample (Holdstock et al., 2000; O'Malley and Maisto, 1985; Savoie et al., 1988). We treated individual samples as the basic unit of our analyses, yielding our total *k* of 32 samples. When unique samples endorsed multiple measures of subjective alcohol response, we computed a mean effect across all measures. When samples were assessed multiple times—either during a single trial or across multiple trials—we again computed the mean effect across assessments. To compute the sample-size-adjusted mean effect estimate, we used a random-effects model, which allows for random between-sample variance beyond sampling variance (Borenstein et al., 2009). This approach assumes that there is no single true population effect and is recommended for use in reviews that do not summarize a set of virtually identical studies (i.e., where one would expect variability beyond sampling error; Schmidt, 2010).

Between-study moderator analyses—When possible, we used mixed-effects models to independently test the effects of between-study moderators (i.e., gender composition).

³In results not reported here, we found little evidence that risk-group differences differed as a function of peak BAC reached, although we note that participants in most studies reached BACs between .08 g/dl and .11 g/dl, which may have limited our ability to detect any meaningful differences. The results of these analyses are available from the first author upon request.

Within each level of the moderator, the mixed effect model operates under the same assumptions as does the random-effects model. In particular, at each level of the moderator, the model assumes there is random variation in the distribution of effect sizes beyond sampling error. In comparing effects across levels of the moderator, however, the mixed-effects model assumes that the moderator is associated with systematic differences (Borenstein et al., 2009). We additionally retained all previously described model specifications for moderator analyses, including averaging across multiple outcome measures or assessment points within samples to produce single effect sizes for each sample.

Critical tests of the LLRM and DM—The chief goal of this investigation was to quantitatively evaluate the LLRM and DM, which partially overlap but also make some distinctly diverging predictions. The DM predicts that at-risk groups should demonstrate greater subjective stimulation and greater response on the ascending limb of the BAC curve—or, more specifically, greater stimulation on the ascending limb of the BAC curve in particular—whereas the LLRM predicts that at-risk groups should demonstrate lower response regardless of BAC limb or sedation versus stimulation. Testing these predictions presented an analytic challenge in that many studies compared groups on both BAC curve limbs and on measures of both stimulation and sedation, resulting in a violation of the assumption of independence of effect sizes. Although there are methods available for multivariate meta-analyses, these approaches require information about correlations among outcome measures not available here and may be susceptible to bias when different studies measure different outcomes (e.g., Raudenbush et al., 1988). Because we are aware of no appropriate method to test the within-study moderation effects hypothesized by the DM, we estimated effect sizes for group differences in sedation and stimulation (and on the ascending and descending limbs) separately. We therefore estimated eight distinct effects to compare the LLRM and DM: group differences in sedation and stimulation, group differences on the ascending and descending limbs, and group differences in sedation and stimulation within each limb.

Publication bias—Meta-analyses, like all reviews, are potentially subject to publication bias (i.e., the file-drawer problem). Studies generating smaller effect sizes are less likely to find significance. If studies with non-significant findings are more likely to go unpublished, then the published effect sizes available for meta-analysis may be biased toward overestimating the mean effect size (Rosenthal and DiMatteo, 2001). For all mean effect sizes that were significantly different from zero, we therefore calculated Rosenthal's (1979) fail-safe N , which estimates the number of additional null findings (from hypothetical unpublished studies) necessary to render the mean effect non-significant. The fail-safe N serves as an indicator of the likelihood that the observed effect is not due to publication bias.

Results

Comparisons for Family History

Overall effect size—In the 19 FH comparisons, FH+ status was associated with a lower overall subjective response to alcohol (i.e., across stimulation, sedation and other measures and across both limbs and the peak of the BAC curve), $g = -0.24$ (95% CI: $-0.49, 0.00$). That is, FH+ participants reported lower subjective response relative to FH– participants, although this effect was small in size. Beyond the mean point estimate of effect size, however, there was significant heterogeneity in effect sizes across studies, $Q_{\text{within}}(18) = 42.51, p = .001, I^2 = 57.66$. As indicated by the I^2 statistic, between-study variability accounted for 58% of the variance in effect sizes. Rosenthal's (1979) fail-safe N indicated that an additional 29 samples (i.e., more than 1.5 times the number of included samples)

with null findings would be necessary to render the overall effect non-significantly different from zero.

The Low Level of Response Model (LLRM) and Differentiator Model (DM) were originally developed to explain differences in subjective response among FH+ *men*. As would be expected by both models, sample gender significantly affected the size of the FH difference, $Q_{\text{between}}(1) = 4.99, p = .03$. In male samples, subjective responses were approximately 0.53 standard deviations lower among FH+ relative to FH−, $g = -0.53$ (95% CI: −0.96, −0.10), although significant between-study heterogeneity remained, $Q_{\text{within}}(9) = 25.88, p = .002, I^2 = 65.23$. For male samples only, the fail-safe N was 38. In contrast, there was very little effect of FH in samples containing women, $g = 0.01$ (95% CI: −0.19, 0.21), nor was there significant heterogeneity across studies, $Q_{\text{within}}(8) = 8.27, p = .41, I^2 = 3.21$.

Critical tests of the LLRM and DM—The models critically differ in that the DM but not the LLRM predicts greater response to alcohol among FH+ individuals on the ascending limb of the BAC curve. In studies that included measurements (stimulant, sedative, or other) on the ascending limb, there was a small, non-significant, negative effect of FH+ on subjective response, $g = -0.20$ (95% CI: −0.48, 0.07), along with significant between-study variability, $Q_{\text{within}}(11) = 22.23, p = .02, I^2 = 50.52$. See Table 3. The weighted mean effect on the descending limb was similar in size, $g = -0.20$ (95% CI: −0.39, −0.01), although the effect was statistically significant (i.e., different from zero) and did not significantly vary across studies, $Q_{\text{within}}(14) = 16.28, p = .30, I^2 = 14.02$. However, the fail-safe N for the descending limb was only three. In sum, limiting comparisons to the ascending and descending limbs provided some support for the LLRM but not for the acute sensitization component of the DM, in that FH+ groups did not report greater response on the ascending limb.

Crucial to the DM is the notion that at-risk individuals experience the positively reinforcing effects of alcohol more strongly but the aversive effects more weakly. Thus, another hypothesis generated from the DM but not the LLRM is that FH+ groups should respond more to the stimulant effects of alcohol relative to FH− groups. In the samples that assessed subjective stimulation (across the BAC curve), however, there was a moderate—but not significantly different from zero—effect in the opposite direction, with FH+ participants reporting less stimulation, $g = -0.46$ (95% CI: −0.94, 0.02). This effect was similar to that found in samples assessing subjective sedation, $g = -0.32$ (95% CI: −0.70, 0.06). There was significant heterogeneity in effect sizes for both stimulation and sedation across studies, $Q_{\text{within}}(5) = 13.62, p = .02, I^2 = 63.30$ and $Q_{\text{within}}(10) = 34.83, p < .001, I^2 = 71.29$, respectively.

A third and more specific prediction from the DM is that, relative to FH− groups, FH+ groups might respond more to the stimulant effects of alcohol on the ascending limb of the BAC curve in particular. In samples that assessed stimulant response on the ascending limb, however, there was a small-to-moderate, non-significant effect in the opposite direction, $g = -0.37$ (95% CI: −0.93, 0.20). In samples that assessed stimulant response on the descending limb, the mean effect size was also in the opposite direction, moderate, and not significantly different from zero, $g = -0.49$ (95% CI: −1.02, 0.05). Additionally, there was significant heterogeneity in stimulation effect sizes on the ascending and descending limbs of the BAC curve, $Q_{\text{within}}(3) = 11.06, p = .01, I^2 = 72.89$ and $Q_{\text{within}}(5) = 16.78, p = .01, I^2 = 70.21$, respectively. As shown in Table 4, effect-size estimates for sedation similarly did not appear to differ across the ascending and descending limbs, although there was significant heterogeneity across studies on the ascending, $Q_{\text{within}}(6) = 15.59, p = .02, I^2 = 61.51$, but not the descending, $Q_{\text{within}}(7) = 12.38, p = .09, I^2 = 43.43$, limb.

Comparisons for Typical Alcohol Consumption

Overall effect size—In the 13 samples comparing participants as a function of typical alcohol consumption, subjective alcohol response (i.e., on stimulant, sedative, and other measures across the BAC curve) did not differentiate heavier from lighter drinkers, $g = -0.10$ (95% CI: $-0.34, 0.14$). That is, in contrast to the comparisons for FH, the overall effect of typical consumption was very small and not significantly different from zero. Beyond the mean effect size, however, there was moderate heterogeneity across studies, $Q_{\text{within}}(12) = 21.41, p = .05, I^2 = 43.95$. Neither the LLRM nor DM makes specific predictions regarding the effect of gender on differences between lighter and heavier drinkers, and a test of moderation revealed no effect of gender, $Q_{\text{between}}(1) = 0.20, p = .66$.

Critical tests of the LLRM and DM—One prediction from the DM is that heavier drinkers should experience greater subjective response on the ascending limb. In those samples testing comparisons (stimulant, sedative, or other) on the ascending limb, however, heavier drinkers reported somewhat lower response, although this effect was not significantly different from 0, $g = -0.06$ (95% CI: $-0.33, 0.22$), and varied significantly across studies, $Q_{\text{within}}(11) = 23.13, p = .02, I^2 = 52.44$. See Table 3. Comparisons on the descending limb resulted in a similar effect, $g = -0.08$ (95% CI: $-0.32, 0.17$), although the size of the effect did not vary significantly across studies, $Q_{\text{within}}(8) = 9.02, p = .34, I^2 = 1.28$.

Whereas the DM would predict stronger response on measures of stimulation and lower response on measures of sedation among heavier drinkers, the LLRM would predict lower response on both types of effects among heavier drinkers. We found clear support for this second DM prediction in that heavier drinkers reported greater stimulation, $g = 0.45$ (95% CI: $0.05, 0.86$), but lower sedation, $g = -0.40$ (95% CI: $-0.63, -0.18$), across the BAC curve. The stimulation effect varied moderately across studies, $Q_{\text{within}}(7) = 18.62, p = .01, I^2 = 62.40$, whereas the sedation effect did not, $Q_{\text{within}}(6) = 3.92, p = .67, I^2 = 0.00$. Fail-safe N 's for the stimulation and sedation effects were 18 and 17, respectively.

Third, the DM may also be interpreted as predicting that heavier drinkers would respond more than lighter drinkers to the stimulant effects of alcohol on the ascending limb of the BAC curve in particular. We found some support for this proposition in that, relative to lighter drinkers, heavier drinkers on average reported moderately and significantly greater stimulation on the ascending limb, $g = 0.53$ (95% CI: $0.15, 0.91$), whereas the stimulation effect on the descending limb was small-to-moderate and not significantly different from zero, $g = 0.34$ (95% CI: $-0.13, 0.80$). In addition, there was moderate between-study heterogeneity in stimulation differences on the ascending and descending limbs, although heterogeneity on the descending limb did not reach significance, $Q_{\text{within}}(7) = 16.44, p = .02, I^2 = 57.43$ and $Q_{\text{within}}(5) = 10.37, p = .07, I^2 = 51.76$, respectively. The fail-safe N for differences in stimulation on the ascending limb was 28. As shown in Table 4, heavier drinkers reported moderately and significantly less sedation in samples assessed on the ascending limb and in samples assessed on the descending limb, and there was no heterogeneity across studies, $Q_{\text{within}}(6) = 8.33, p = .22, I^2 = 27.94$, and $Q_{\text{within}}(3) = 0.94, p = .82, I^2 = 0.00$, respectively. Fail-safe N s for sedation on the ascending and descending limbs were 26 and 2, respectively.

Finally, because these stimulation differences appeared unique relative to the effects reported for FH comparisons, we tested whether comparison type moderated stimulation differences when aggregating samples across FH and typical consumption comparisons. As expected, across the ascending and descending limbs of the BAC curve, the stimulation difference in typical consumption comparisons was significantly greater than the stimulation difference in FH comparisons, $Q_{\text{between}}(1) = 8.18, p = .004$. Further, when examined

separately, stimulation differences in typical consumption comparisons were significantly greater than differences in FH comparisons on both the ascending and descending limbs, $Q_{\text{between}}(1) = 6.60, p = .01$, and $Q_{\text{between}}(1) = 5.16, p = .02$, respectively.

Discussion

This meta-analytic review of three decades of research found some support for each of the two major theories of subjective response to alcohol. First, the results of FH comparisons largely matched the predictions of the LLRM. Specifically, FH+ groups experienced reduced overall subjective response relative to FH− groups. This difference did not appear to differ as a function of the stimulant or sedative effects of alcohol, although it was more statistically reliable on the descending limb of the BAC curve (i.e., the acute tolerance effect). Finally, the difference was most evident among men. FH+ men responded more than half a standard deviation less than did FH− men, but this association was diminished when women were included in comparisons. In sum, FH+ men displayed a lower overall level of response to alcohol, just as predicted by the LLRM, and we found no evidence of greater response among FH+ groups under any conditions.

Although as described previously the evidence from FH comparisons aligns more strongly with the LLRM than the DM, we found considerable support for predictions of the DM in studies of typical alcohol consumption. Specifically, heavier drinkers of both genders responded 0.4 standard deviations less than did lighter drinkers on measures of sedation but nearly half a standard deviation *more* on measures of stimulation. That is, heavier drinkers experienced the stimulant effects of alcohol to a greater extent than did lighter drinkers. Further, although sedation effect sizes were similar in magnitude and significance across the ascending and descending limbs of the BAC curve, the stimulation difference appeared more pronounced on the ascending limb. Whereas these findings are largely in line with the DM, they cannot be explained by the LLRM. In considering effect sizes for stimulation and sedation responses within limbs of the BAC curve, however, it is important to note that these analyses required that we divide the included samples into relatively small sets (see Table 4). Given the between-study variability observed here, we caution that there may be instability in these effect-size estimates.

Remaining Issues in the Reviewed Literature: Suggestions for Future Research

Several lingering issues remain in the accumulated evidence presented here. Because some have recently been addressed in depth elsewhere (Morean and Corbin, 2010), we discuss them only briefly. First, it is widely understood that a failure to support a prediction is not equivalent to a disconfirmation, and this distinction is particularly relevant to the FH findings reviewed here. This meta-analysis included a relatively small number of FH comparisons on measures of stimulant alcohol effects, only four of which included assessments on the ascending limb of the BAC curve. We found no evidence of greater subjective responses among FH+ groups in any of our analyses, but this pattern does not rule out the possibility that further study will provide support for the DM under these specific conditions.

Second, because of legal and ethical concerns, the vast majority of alcohol-challenge studies have excluded participants under the age of 21. Thus, although we refer to FH+ and heavier-drinking groups as 'at risk,' some of those at highest risk are likely excluded from this paradigm because they would have already met criteria for alcohol dependence prior to age 21 (e.g., Li et al., 2004). Future research employing alternative paradigms could strengthen existing support for the LLRM and DM. One such alternative involves retrospective assessments of subjective response to early drinking experiences (e.g., Schuckit et al., 1997),

but others—potentially including animal models or structured interviews or experience sampling methods among youth—should be considered as well.

Third, beyond the point estimates of effect size reported above, there was often substantial heterogeneity across studies. Although some of this variability could be explained by differences in gender composition, assessment of stimulation or sedation, and limbs of the BAC curve, other unmeasured differences between studies may have also contributed to effect heterogeneity. For example, studies differed on definitions of risk status, alcohol dosage, and other design components. Although we found little evidence that dosage moderated risk-group differences, the limited descriptions of other study factors—including participant ethnicities, dose pacing, time of day, and other contextual variables—presented in many studies precluded quantitative evaluations. Given that social context can increase subjective stimulant response to alcohol (Ray et al., 2010) and that some East Asians report greater subjective response as a function of genetic differences in alcohol metabolism (Hendershot et al., 2009), further study of these potentially important factors is warranted. As recommended by Morean and Corbin (2010), the use of standardized alcohol-administration procedures and risk-group categorization methods (e.g., binge drinking; Wechsler and Isaac, 1992)—along with validated measures of subjective stimulation and sedation (Martin et al., 1993; Ray et al., 2009) and placebo-controlled designs to rule out expectancy explanations—will speed advancements in this area.

Finally, the reviewed studies were largely underpowered, which can explain both failures to replicate previous findings and aberrant large effects (Maxwell, 2004). The average sample included in the meta-analysis comprised 41 total participants (i.e., 20.5 participants per group). At 80% power, this sample size would only be sensitive to group differences greater than or equal to 0.90 standard deviations, effects far larger than the mean sizes estimated here. Future alcohol-challenge studies will require larger samples.

Theoretical Implications

Outstanding questions notwithstanding, the results of this meta-analysis have several substantial implications for models of subjective response to alcohol. Schuckit and colleagues (2010) recently described differences in subjective stimulant response as a risk factor separate from the overall level of response, one of “many interesting and potentially important additional characteristics that might indicate a vulnerability toward later alcoholism” (p. 203). The evidence summarized here illustrates that these authors may have described an important distinction. The low sensitivity to alcohol found among FH+ men (and described by the LLRM) may in fact be a separate risk factor from the increased stimulation and decreased sedation found in heavy drinkers of both genders (and described by the DM). Further research is needed, however, to determine whether they can co-occur in the same individuals and how they might interact with one another.

The mechanisms through which these different subjective response profiles contribute to the development of AUDs also may differ among the two types of at-risk groups, and this area is ripe for additional study. A low level of overall response to alcohol appears to represent an important component of inherited risk for AUDs, with prospective studies providing additional support for this view (e.g., Schuckit, 1994; Schuckit and Smith, 1996; Schuckit and Smith, 2000; Schuckit and Smith, 2001; Schuckit et al., 2007; Trim et al., 2009). Less is known, however, about why this intermediate phenotype confers risk. The LLRM proposes that FH+ men require greater alcohol consumption to achieve intoxication, which motivates them to drink more heavily (e.g., Schuckit, 2009), but to our knowledge no study has yet specifically evaluated this hypothesis.

Heavier drinkers of both genders, in contrast, may be motivated to drink because they find alcohol less aversive and more pleasurable, perhaps particularly on the ascending limb of the BAC curve. This finding suggests a possible clarification of the Differentiator Model, in which the quality of the subjective response (i.e., stimulation versus sedation) is given more etiological prominence. As discussed previously, the alcohol-challenge paradigm cannot determine the direction of the association between heavier drinking and subjective response to alcohol. There is, however, increasing evidence that greater response to the stimulant effects of alcohol predicts future drinking, suggesting that, at the very least, it may contribute to the maintenance of heavy drinking patterns. Young adults who experience greater stimulant effects early in a drinking episode go on to drink more in that episode (Corbin et al., 2008; Ray et al., 2010; Wetherill and Fromme, 2009). Additionally, evidence from retrospective reports suggests that greater early stimulant response may predict greater consumption later in life (Chung and Martin, 2009). Further, Thomas and colleagues (2004) found greater stimulant response to alcohol challenge among alcohol dependent individuals relative to social drinkers. Prospective research is needed to begin testing the mechanisms through which stimulant and sedative responses could contribute to problematic drinking outcomes.

Moreover, research capitalizing on the increasing availability of genotyping techniques presents another promising avenue for identifying the physiological and neurological underpinnings of these subjective responses. Some studies have identified candidate genes related to subjective stimulant (e.g., Ray and Hutchison, 2004; Ray et al., 2010) and sedative responses (e.g., Corbin et al., 2006; Hinkers et al., 2006; Hu et al., 2005; Lind et al., 2008; Schuckit et al., 1999). In addition to providing evidence that subjective stimulant and sedative responses to alcohol may be inherited risk factors, this line of research has the potential to clarify the ways in which the two responses are similar and distinct.

Limitations

Several limitations of our analytic approach may constrain the conclusions we can draw from this review. First, although techniques have been developed to adjust estimates of effect size for error in the measurement of study variables (Schmidt, 2010), reliability data for too many of the measures included in this meta-analysis was lacking, precluding this adjustment. The mean effect sizes reported above may therefore represent lower-bound estimates of differences in subjective response (Schmidt, 2010). Second, like all reviews, this meta-analysis was potentially subject to publication bias. Consistent with the competing theories and nontrivial number of null effects found in included studies, however, tests of publication bias suggested that the primary findings reported here, including the overall FH difference and the stimulation and sedation differences in comparisons for typical consumption, were robust to any potential bias. Finally, we were only able to include a subset of all relevant alcohol-challenge studies identified in our literature search. We do not believe that this restriction impaired our ability to draw valid conclusions for two reasons. First, we were ultimately able to include 73% of eligible studies. Second, our use of the random-effects model permits us to generalize our findings to studies not included in our analyses (Schmidt, 2010). Nevertheless, both this limitation and the considerable heterogeneity among included studies suggest that conclusions in this research area are not yet definitive.

Conclusions

The reviewed research suggests that both the LLRM and the DM may be useful in understanding subjective responses. Thirty years of research have provided considerable evidence that FH+ men respond less strongly to the effects of alcohol, perhaps particularly on the descending limb of the BAC curve, and some prospective evidence suggests that this

risk factor may predict eventual AUD diagnosis. These findings are consistent with a low level of response as an intermediate phenotype for the development of AUDs. In contrast, heavier drinkers showed distinctly more subjective stimulation and distinctly less sedation. Whether these effects reflect inborn, inherited factors and whether they prospectively predict increased risk for AUDs remains to be determined. Although previous efforts have treated the LLRM and DM as competing theoretical approaches, the results of this quantitative review suggest that they may describe two separate subjective response risk factors, each with its own etiological pathway toward AUDs.

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References

References included in the meta-analysis are marked with asterisks.

- Borenstein, M.; Hedges, L.; Higgins, J.; Rothstein, H. *Comprehensive Meta-Analysis*. 2. Biostat; Englewood, NJ: 2005.
- Borenstein, M.; Hedges, L.; Higgins, J.; Rothstein, H. *Introduction to meta-analysis*. John Wiley and Sons, Ltd; West Sussex, United Kingdom: 2009.
- *. Brumback T, Cao D, King A. Effects of alcohol on psychomotor performance and perceived impairment in heavy binge social drinkers. *Drug Alcohol Depen*. 2007; 91:10–17.
- *. Brunelle C, Barrett SP, Pihl RO. Relationship between the cardiac response to acute intoxication and alcohol-induced subjective effects throughout the blood alcohol concentration curve. *Hum Psychopharmacol Clin Exp*. 2007; 22:437–443.
- *. Chiu T-M, Mendelson JH, Sholar MB, Mutschler NH, Wines JD, Hesselbrock VM, Mello NK. Brain alcohol detectability in human subjects with and without a paternal history of alcoholism. *J Stud Alcohol*. 2004; 65:16–21. [PubMed: 15000499]
- Chung T, Martin C. Subjective stimulant and sedative effects of alcohol during early drinking experiences predict alcohol involvement in treated adolescents. *J Stud Alcohol Drugs*. 2009; 70:660–667. [PubMed: 19737489]
- Cohen, J. *Statistical power analysis for the behavioral sciences*. 2. Lawrence Erlbaum Associates; Hillsdale, NJ: 1988.
- Corbin WR, Fromme K, Bergeson SE. Preliminary data on the association among the serotonin transporter polymorphism, subjective alcohol experiences, and drinking behavior. *J Stud Alcohol*. 2006; 67:5–13. [PubMed: 16536124]
- Corbin WR, Gearhardt A, Fromme K. Stimulant alcohol effects prime within session drinking behavior. *Psychopharmacology*. 2008; 197:327–337. [PubMed: 18084744]
- *. Earleywine M. Measurement issues in the assessment of acute changes in responses to alcohol. *Exp Clin Psychopharm*. 1995; 3:382–388.
- Ehlers CL, Schuckit MA. Evaluation of EEG alpha activity in sons of alcoholics. *Neuropsychopharmacol*. 1991; 4:199–205.
- *. Eng MY, Schuckit MA, Smith TL. The level of response to alcohol in daughters of alcoholics and controls. *Drug Alcohol Depen*. 2005; 79:83–93.
- *. Erblich J, Earleywine M, Erblich B, Bovbjerg DH. Biphasic stimulant and sedative effects of ethanol: Are children of alcoholics really different? *Addict Behav*. 2003; 28:1129–1139. [PubMed: 12834655]
- *. Evans SM, Levin FR. Response to alcohol in females with a paternal history of alcoholism. *Psychopharmacology*. 2003; 169:10–20. [PubMed: 12721780]
- *. Evans SM, Levin FR. Differential response to alcohol in light and moderate female social drinkers. *Behav Pharmacol*. 2004; 15:167–181. [PubMed: 15187575]

- *. Hammersley R, Finnigan F, Millar K. Individual differences in the acute response to alcohol. *Pers Indiv Differ*. 1994; 17:497–510.
- Heath AC, Madden PAF, Bucholz KK, Dinwiddie SH, Slutske WS, Bierut LJ, Rohrbach JW, Statham DJ, Dunne MP, Whitfield JB, Martin NG. Genetic differences in alcohol sensitivity and the inheritance of alcoholism risk. *Psychol Med*. 1999; 29:1069–1081. [PubMed: 10576299]
- Hendershot CS, Collins SE, George WH, Wall TL, McCarthy DM, Liang T, Larimer ME. Associations of ALDH2 and ADH1B genotypes with alcohol-related phenotypes in Asian young adults. *Alcohol: Clin Exp Res*. 2009; 33:839–847. [PubMed: 19298323]
- *. Hiltunen AJ. Acute alcohol tolerance in social drinkers: Changes in subjective effects dependent on the alcohol dose and prior alcohol experience. *Alcohol*. 1997; 14:373–378. [PubMed: 9209553]
- Hinckes AS, Laucht M, Schmidt MH, Mann KF, Schumann G, Schuckit MA, Heinz A. Low level of response to alcohol as associated with serotonin transporter genotype and high alcohol intake in adolescents. *Biol Psychiat*. 2006; 60:282–287. [PubMed: 16497275]
- Hines LM, Ray L, Hutchison KE, Tabakoff B. Alcoholism: The dissection for endophenotypes. *Dialogues Clin Neurosci*. 2005; 7:153–163. [PubMed: 16262210]
- *. Holdstock L, King AC, de Wit H. Subjective and objective responses to ethanol in moderate/heavy and light social drinkers. *Alcohol Clin Exp Res*. 2000; 24:789–794. [PubMed: 10888066]
- Hu X, Oroszi G, Chun J, Smith TL, Goldman D, Schuckit MA. An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. *Alcohol Clin Exp Res*. 2005; 29:8–16. [PubMed: 15654286]
- Judd LL, Hubbard RB, Janowsky DS, Huey LY, Atewall PA. The effect of lithium carbonate on affect, mood, and personality of normal subjects. *Arch Gen Psychiatry*. 1977; 34:346–351. [PubMed: 320956]
- *. King AC, Houle T, de Wit H, Holdstock L, Schuster A. Biphasic alcohol response differs in heavy versus light drinkers. *Alcohol Clin Exp Res*. 2002; 26:827–835. [PubMed: 12068251]
- *. Lex BW, Lukas SE, Greenwald NE, Mendelson JH. Alcohol-induced changes in body sway in women at risk for alcoholism: A pilot study. *J Stud Alcohol*. 1988; 49:346–356. [PubMed: 3172783]
- *. Lex BW, Rhoades EM, Teoh SK, Mendelson JH. Divided attention task performance and subjective effects following alcohol and placebo: Differences between women with and without a family history of alcoholism. *Drug Alcohol Depen*. 1994; 35:95–105.
- Lind PA, MacGregor S, Montgomery GW, Heath AC, Martin NG, Whitfield JB. Effects of GABRA2 variation on physiological, psychomotor and subjective responses in the Alcohol Challenge Twin Study. *Twin Res Hum Genet*. 2008; 11:174–182. [PubMed: 18361719]
- Li T-K, Hewitt BG, Grant BF. Alcohol use disorders and mood disorders: A National Institute on Alcohol Abuse and Alcoholism perspective. *Biol Psychiat*. 2004; 56:718–720. [PubMed: 15556112]
- Liu IC, Blacker DL, Xu R, Fitzmaurice G, Lyons MJ, Tsuang MT. Genetic and environmental contributions to the development of alcohol dependence in male twins. *Arch Gen Psychiatry*. 2004; 61:897–903. [PubMed: 15351768]
- *. Marczinski CA, Combs SW, Fillmore MT. Increased sensitivity to the disinhibiting effects of alcohol in binge drinkers. *Psychol Addict Behav*. 2007; 21:346–354. [PubMed: 17874885]
- *. Marczinski CA, Fillmore MT. Acute alcohol tolerance on subjective intoxication and simulated driving performance in binge drinkers. *Psychol Addict Behav*. 2009; 23:238–247. [PubMed: 19586140]
- *. Martin CS, Earleywine M, Musty RE, Perrine MW. Development and validation of the Biphasic Alcohol Effects Scale. *Alcohol Clin Exp Res*. 1993; 17:140–146. [PubMed: 8452195]
- Martin WR, Sloan JW, Sapira JD, Jasinski DR. Physiologic, subjective and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine and methylphenidate in man. *Clin Pharmacol Ther*. 1971; 12:245–258. [PubMed: 5554941]
- Maxwell SE. The persistence of underpowered studies in psychological research: Causes, consequences, and remedies. *Psychol Methods*. 2004; 9:147–163. [PubMed: 15137886]
- McNair, DM.; Lorr, M.; Droppleman, LF. Manual for the Profile of Mood States. Educational and Industrial Testing Service; San Diego, CA: 1971.

- *. Monteiro MG, Klein JL, Schuckit MA. High levels of sensitivity to alcohol in young adult Jewish men: A pilot study. *J Stud Alcohol*. 1991; 52:464–469. [PubMed: 1943102]
- Morean ME, Corbin WR. Subjective response to alcohol: A critical review of the literature. *Alcohol Clin Exp Res*. 2010; 34:385–395. [PubMed: 20028359]
- *. Moss HB, Yao JK, Maddock JM. Responses by sons of alcoholic fathers to alcoholic and placebo drinks: Perceived mood, intoxication, and plasma prolactin. *Alcohol Clin Exp Res*. 1989; 13:252–257. [PubMed: 2658666]
- *. Nagoshi CT, Wilson JR. Influence of family alcoholism history on alcohol metabolism, sensitivity, and tolerance. *Alcohol Clin Exp Res*. 1987; 11:392–398. [PubMed: 3307511]
- Newlin DB, Renton RM. High risk groups often have higher levels of alcohol response than low risk: The other side of the coin. *Alcohol Clin Exp Res*. 2010; 34:199–202. [PubMed: 19951303]
- Newlin DB, Thomson JB. Alcohol challenge with sons of alcoholics: A critical review and analysis. *Psychol Bull*. 1990; 108:383–402. [PubMed: 2270234]
- *. O'Malley SS, Maisto SA. Effects of family drinking history and expectancies on responses to alcohol in men. *J Stud Alcohol*. 1985; 46:289–297. [PubMed: 4033129]
- *. Pedersen SL, McCarthy DM. An examination of subjective response to alcohol in African-Americans. *J Stud Alcohol Drugs*. 2009; 70:288–295. [PubMed: 19261241]
- Pollock VE. Meta-analysis of subjective sensitivity to alcohol in sons of alcoholics. *Am J Psychiatry*. 1992; 149:1534–1538. [PubMed: 1415821]
- *. Pollock VE, Teasdale TW, Gabrielli WF, Knop J. Subjective and objective measures of response to alcohol among young men at risk for alcoholism. *J Stud Alcohol*. 1986; 47:297–304. [PubMed: 3747531]
- Prescott CA, Kendler KS. Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. *Am J Psychiatry*. 1999; 156:34–40. [PubMed: 9892295]
- Raudenbush SW, Becker BJ, Kalaian H. Modeling multivariate effect sizes. *Psychol Bull*. 1988; 103:111–120.
- Ray LA, Hutchison KE. A polymorphism of the mu-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans. *Alcohol Clin Exp Res*. 2004; 28:1789–1795. [PubMed: 15608594]
- *. Ray LA, MacKillop J, Leventhal A, Hutchison KE. Catching the alcohol buzz: An examination of the latent factor structure of subjective intoxication. *Alcohol Clin Exp Res*. 2009; 33:2154–2161. [PubMed: 19764932]
- Ray LA, McGeary J, Marshall E, Hutchison KE. Risk factors for alcohol misuse: Examining heart rate reactivity to alcohol, alcohol sensitivity, and personality constructs. *Addict Behav*. 2006; 31:1959–1973. [PubMed: 16466861]
- Ray LA, Miranda R, Tidey JW, McGeary JE, MacKillop J, Gwaltney CJ, Rohsenow DJ, Swift RM, Monti PM. Polymorphisms of the mu-opioid receptor and dopamine D4 receptor genes and subjective responses to alcohol in the natural environment. *J Abnorm Psychol*. 2010; 119:115–125. [PubMed: 20141248]
- Rosenthal R. The file drawer problem and tolerance for null results. *Psychol Bull*. 1979; 86:638–641.
- Rosenthal R, DiMatteo MR. Meta analysis: Recent developments in quantitative methods for literature reviews. *Annu Rev Psychol*. 2001; 52:59–82. [PubMed: 11148299]
- *. Savoie TM, Emory EK, Moody-Thomas S. Acute alcohol intoxication in socially drinking female and male offspring of alcoholic fathers. *J Stud Alcohol*. 1988; 49:430–435. [PubMed: 3216646]
- Schmidt F. Detecting and correcting the lies that data tell. *Perspect Psychol Sci*. 2010; 5:233–242.
- *. Schuckit MA. Self-rating of alcohol intoxication by young men with and without family histories of alcoholism. *J Stud Alcohol*. 1980; 41:242–249. [PubMed: 7374142]
- *. Schuckit MA. Subjective responses to alcohol in sons of alcoholics and control subjects. *Arch Gen Psychiatry*. 1984; 41:879–884. [PubMed: 6466047]
- Schuckit MA. Ethanol-induced changes in body sway in men at high alcoholism risk. *Arch Gen Psychiatry*. 1985; 42:375–379. [PubMed: 3977555]

- Schuckit MA. Low level of response to alcohol as a predictor of future alcoholism. *Am J Psychiatry*. 1994; 151:184–189. [PubMed: 8296886]
- Schuckit MA. An overview of genetic influences in alcoholism. *J Subst Abuse Treat*. 2009; 36:S1–S14.
- Schuckit MA, Gold EO. A simultaneous evaluation of multiple markers of ethanol/placebo challenges in sons of alcoholics and controls. *Arch Gen Psychiatry*. 1988; 45:211–216. [PubMed: 3422553]
- Schuckit MA, Gold EO, Croot K, Finn P. P300 latency after ethanol ingestion in sons of alcoholics and in controls. *Biol Psychiat*. 1988a; 24:310–315. [PubMed: 3401524]
- Schuckit MA, Gold EO, Risch SC. Serum prolactin levels in sons of alcoholics and control subjects. *Am J Psychiatry*. 1987a; 144:854–859. [PubMed: 3605397]
- Schuckit MA, Gold EO, Risch SC. Plasma cortisol levels following ethanol in sons of alcoholics and controls. *Arch Gen Psychiatry*. 1987b; 44:942–945. [PubMed: 3675133]
- Schuckit MA, Mazzanti C, Smith TL, Ahmed U, Radel M, Iwata N, Goldman D. Selective genotyping for the role of 5-HT_{2A}, 5-HT_{2C}, and GABA_A6 receptors and the serotonin transporter in the level of response to alcohol: A pilot study. *Biol Psychiat*. 1999; 45:647–651. [PubMed: 10088053]
- Schuckit MA, Risch SC, Gold EO. Alcohol consumption, ACTH level, and family history of alcoholism. *Am J Psychiatry*. 1988b; 145:1391–1395. [PubMed: 2847567]
- Schuckit MA, Smith TL. An 8-year followup of 450 sons of alcoholic and control subjects. *Arch Gen Psychiatry*. 1996; 53:202–210. [PubMed: 8611056]
- Schuckit MA, Smith TL. The relationships of a family history of alcohol dependence, a low level of response to alcohol and six domains of life functioning to the development of alcohol use disorders. *J Stud Alcohol*. 2000; 61:827–835. [PubMed: 11188488]
- Schuckit MA, Smith TL. The clinical course of alcohol dependence associated with a low level of response to alcohol. *Addiction*. 2001; 96:903–910. [PubMed: 11399221]
- Schuckit MA, Smith TL, Tipp JE. The Self-Rating of the Effects of Alcohol (SRE) form as a retrospective measure of the risk for alcoholism. *Addiction*. 1997; 92:979–988. [PubMed: 9376780]
- Schuckit MA, Smith TL, Danko GP, Pierson J, Hesselbrock V, Bucholz KK, Kramer J, Kuperman S, Dietiker C, Brandon R, Chan G. The ability of the Self-Rating of the Effects of Alcohol (SRE) Scale to predict alcohol-related outcomes five years later. *J Stud Alcohol Drugs*. 2007; 68:371–378. [PubMed: 17446976]
- *. Schuckit MA, Smith TL, Kalmijn J, Danko GP. A cross-generational comparison of alcohol challenges at about age 20 in 40 father-offspring pairs. *Alcohol Clin Exp Res*. 2005; 29:1921–1927. [PubMed: 16340447]
- Schuckit MA, Smith TL, Trim RS. Letter to the editor. *Alcohol Clin Exp Res*. 2010; 34:203–205.
- Thomas SE, Drobos DJ, Voronin K, Anton RF. Following alcohol consumption, nontreatment-seeking alcoholics report greater stimulation but similar sedation compared with social drinkers. *J Stud Alcohol*. 2004; 65:330–335. [PubMed: 15222589]
- Trim RS, Schuckit MA, Smith TL. The relationships of the level of response to alcohol and additional characteristics to alcohol use disorders across adulthood: A discrete-time survival analysis. *Alcohol Clin Exp Res*. 2009; 33:1562–1570. [PubMed: 19485971]
- Trim RS, Simmons AN, Tolentino NJ, Hall SA, Matthews SC, Robinson SK, Smith TL, Padula CB, Paulus MP, Tapert SF, Schuckit MA. Acute ethanol effects on brain activation in low- and high-level responders to alcohol. *Alcohol Clin Exp Res*. 2010; 34:1162–1170. [PubMed: 20477775]
- *. Vogel-Sprott M, Chipperfield B. Family history of problem drinking among young male social drinkers: Behavioral effects of alcohol. *J Stud Alcohol*. 1987; 48:430–436. [PubMed: 3669669]
- Wechsler H, Isaac N. 'Binge' drinkers at Massachusetts colleges: Prevalence, drinking style, time trends, and associated problems. *J Am Med Assoc*. 1992; 267:2929–2931.
- Wetherill RR, Fromme K. Subjective responses to alcohol prime event-specific alcohol consumption and predict blackouts and hangover. *J Stud Alcohol Drugs*. 2009; 70:593–600. [PubMed: 19515300]

Table 1
Included Studies of Subjective Response to Alcohol Challenge as a Function of Family History of Alcohol Use Disorder

Study	Independent Samples	N	Raw Effect Size <i>g</i> (SE)	Measurement Types	Measure Names	Measurement Limbs	Gender	BAC Level (g/dl)	Figure
Chiu et al. (2004)	-	16	-4.63 (0.96)	Sedation	SHAS	Peak	Male	.10	No
Eng et al. (2005)	-	50	-0.42 (0.28)	Sedation	SHAS	Ascending, Peak	Female	.08	No
Erblich et al. (2003)	-	100	0.02 (0.26)	Sedation, Stimulation	BAES	Ascending, Descending	Mixed	.08	No
Evans & Levin (2003)	-	32	-0.10 (0.36)	Stimulation, Other	DEQ, POMS	Ascending, Peak, Descending	Female	.03, .05, .08	No
Lex et al. (1994)	-	12	-0.33 (0.47)	Sedation	SHAS	Ascending, Descending	Female	.08	Yes
Lex et al. (1988)	-	17	0.84 (0.56)	Sedation	SHAS	Ascending, Descending	Female	.08	Yes
Monteiro et al. (1991)	-	30	-0.67 (0.37)	Sedation	SHAS	Descending	Male	.08	No
Moss et al. (1989)	-	20	0.60 (0.48)	Stimulation, Other	POMS, Intoxication VAS	Ascending, Peak, Descending	Male	.01, .08	Yes
Nagoshi & Wilson (1987)	-	70	0.35 (0.24)	Other	Single-Item Intoxication Scale	Peak	Mixed	.08	No
O'Malley & Maisto (1985)	Low Dose High Dose	16 16	-0.60 (0.49) -0.57 (0.48)	Other Other	Single-Item Intoxication Scale Single-Item Intoxication Scale	Ascending, Descending Ascending, Descending	Male Male	.04 .07	No No
Pedersen & McCarthy (2009)	-	103	0.11 (0.20)	Sedation, Stimulation	BAES	Ascending, Descending	Mixed	.08	No
Pollock et al. (1986)	-	58	-0.34 (0.27)	Other	Single-Item Intoxication Scale	Ascending, Descending	Male	.04	No
Savoie et al. (1988)	Male Female	12 12	-0.47 (0.57) -0.22 (0.53)	Stimulation Stimulation	Sensation Scale-Stimulant Sensation Scale-Stimulant	Peak, Descending Peak, Descending	Male Female	.09 .08	No No
Schuckit (1980)	-	40	-0.65 (0.32)	Sedation	SHAS	Ascending, Peak, Descending	Male	.08	Yes
Schuckit (1984)	-	46	-0.33 (0.29)	Sedation	SHAS	Ascending, Descending	Male	.08, .11	Yes
Schuckit et al. (2005)	-	40	-0.27 (0.32)	Sedation	SHAS	Peak, Descending	Mixed	.08	No
Vogel-Sprott & Chipperfield (1987)	-	26	-0.13 (0.38)	Sedation	SHAS	Peak	Male	.08	No

Note. Independent samples column indicates studies in which more than one unique sample was included in the meta-analysis. Figure column indicates samples for which data was collected from figures. Other measurement type refers to measures that could not be classified as stimulation or sedation. BAC = Blood alcohol concentration. BAES = Biphasic Alcohol Effects Scale. DEQ = Drug Effects Questionnaire. POMS = Profile of Mood States. SHAS = Subjective High Assessment Scale. VAS = Visual Analogue Scale.

Table 2
Included Studies of Subjective Response to Alcohol Challenge as a Function of Typical Alcohol Consumption

Study	Independent Samples	N	Raw Effect Size g (SE)	Measurement Types	Measure Names	Measurement Limbs	Gender	BAC Level (g/dl)	Figure
Brumback et al. (2007)	-	132	-0.45 (0.18)	Other	Impairment	Ascending, Descending	Mixed	.04, .09	No
Brunelle et al. (2007)	-	39	-0.12 (0.33)	Sedation, Stimulation	BAES	Ascending, Descending	Male	.07	No
Earleywine (1995)	-	20	0.96 (0.52)	Stimulation	BAES	Ascending, Peak, Descending	Male	.05	No
Evans & Levin (2004)	-	30	-0.03 (0.36)	Stimulation, Other	DEQ, POMS	Ascending, Peak, Descending	Female	.03, .05, .08	No
Hammersley et al. (1994)	-	60	-0.62 (0.27)	Other	Single-Item Intoxication Scale	Peak	Male	.08	No
Hiltunen (1997)	-	10	-0.04 (0.60)	Other	Intoxication VAS	Ascending, Descending	Male	.05, .10	Yes
Holdstock et al. (2000)	Holdstock & de Wit King	18 18	0.03 (0.48) 0.32 (0.46)	Sedation, Stimulation Sedation, Stimulation	ARCI BAES	Ascending, Descending Ascending, Descending	Mixed Male	.08 .06	Yes Yes
King et al. (2002)	-	34	-0.11 (0.35)	Sedation, Stimulation, Other	ARCI, BAES, DEQ	Ascending, Peak, Descending	Mixed	.04, .08	No
Marczinski et al. (2007)	-	32	0.67 (0.37)	Sedation, Stimulation	BAES	Ascending	Mixed	.08	Yes
Marczinski & Fillmore (2009)	-	28	-0.13 (0.39)	Other	Single-Item Intoxication Scale	Ascending, Descending	Mixed	.09	No
Martin et al. (1993)	-	42	-0.77 (0.34)	Sedation	BAES	Ascending	Mixed	.06	No
Ray et al. (2009)	-	135	0.06 (0.18)	Sedation, Stimulation, Other	BAES, POMS, SHAS	Ascending, Peak	Mixed	.02, .04, .06	No

Note. Independent samples column indicates studies in which more than one unique sample was included in the meta-analysis. Figure column indicates samples for which data was collected from figures. ARCI = Addiction Research Center Inventory. Other measurement type refers to measures that could not be classified as stimulation or sedation. BAC = Blood alcohol concentration. BAES = Biphasic Alcohol Effects Scale. DEQ = Drug Effects Questionnaire. POMS = Profile of Mood States. VAS = Visual Analogue Scale.

Table 3
Subjective Response to Alcohol by Measure Type and BAC Curve Limb

Effect Category	Comparisons for Family History			Comparisons for Typical Consumption		
	<i>g</i>	95% CI of <i>g</i>	<i>k</i>	<i>n</i>	<i>g</i>	95% CI of <i>g</i>
Limb of the BAC Curve						
Ascending	-0.20	-0.48, 0.07	12	510	-0.07	-0.32, 0.18
Descending	-0.20*	-0.39, -0.01	15	554	-0.13	-0.33, 0.08
Measure Type						
Stimulation	-0.46	-0.94, 0.02	6	279	0.45*	0.05, 0.86
Sedation	-0.32	-0.70, 0.06	11	480	-0.40*	-0.63, -0.18

Note. Positive *g* values indicate greater alcohol response among participants at greater risk (i.e., positive family history of AUDs or heavier alcohol consumption). Bolded rows reflect critical tests of the Low Level of Response and Differentiator Models (i.e., where the predictions of the two models differ). Measure type estimates include effect sizes aggregated across limbs of the BAC curve, and limb of the BAC curve estimates include effect sizes aggregated across measure types. *k* = number of included samples.

* $p < .05$.

Table 4
Subjective Stimulation and Sedation Responses within Limb of the BAC Curve

Effect Category	Comparisons for Family History			Comparisons for Typical Consumption		
	<i>g</i>	95% CI of <i>g</i>	<i>k</i>	<i>n</i>	<i>g</i>	95% CI of <i>g</i>
Stimulation						
Ascending limb	-0.37	-0.93, 0.20	4	255	0.53*	0.15, 0.91
Descending limb	-0.49	-1.02, 0.05	6	279	0.34	-0.13, 0.80
Sedation						
Ascending limb	-0.17	-0.54, 0.21	7	368	-0.50*	-0.79, -0.21
Descending limb	-0.17	-0.47, 0.12	8	388	-0.44*	-0.82, -0.06

Note. Positive *g* values indicate greater alcohol response among participants at greater risk (i.e., FH+ or heavier alcohol consumption). Bolded row reflects critical test of the Low Level of Response and Differentiator Models (i.e., where the predictions of the two models differ). *k* = number of included samples.

* *p* < .05.