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Title: Comparison of Subjective Responses to Oral and Intravenous Alcohol Administration under Similar Systemic Exposures

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### Abstract

*Objective:* To test whether an individual's subjective responses to alcohol are similar when the breath alcohol concentration (BrAC) trajectory resulting from oral administration is matched by intravenous administration. *Background:* Individuals perceive the effects of alcohol differently, and the variation is commonly used in research assessing the risk for developing an alcohol use disorder. Such research is supported by both oral and intravenous alcohol administration techniques, and any differences attributable to the route employed should be understood. *Methods:* We conducted a 2-session, within-subject study in 44 young adult, healthy, non-dependent drinkers (22 females and 22 males). In the first session, subjects ingested a dose of alcohol which was individually calculated, on the basis of total body water, to yield a peak BrAC near 80 mg/dl, and the resulting BrAC trajectory was recorded. A few days later, subjects received an intravenous alcohol infusion rate profile, pre-computed to replicate each individual's oral alcohol BrAC trajectory. In both sessions, we assessed 4 subjective responses to alcohol: SEDATION, SIMULATION, INTOXICATION, and HIGH; at baseline and frequently for 4 hours. We compared the individuals' baseline-corrected responses at peak BrAC and at half-peak BrAC on both the ascending and descending limbs. We also computed and compared Pearson-product moment correlations of responses by route of administration, the Mellanby measure of acute adaptation to alcohol, and the area under the entire response curve for each subjective response. *Results:* No significant differences in any measure could be attributed to the route

of alcohol administration. Eleven of 12 response comparisons were significantly correlated across the routes of alcohol administration, with 9 surviving correction for multiple measures, as did the Mellanby effect and area under the response curve correlations. *Conclusion:* The route of alcohol administration has a minimal effect on subjective responses to alcohol when an individual's BrAC exposure profiles are similar.

Key Words: Subjective Response, Mellanby, Tolerance, Route of Administration

## Introduction

Subjective responses to alcohol change with progression along the alcohol exposure trajectory that follows alcohol administration. Variation across participants in the magnitude of subjective responses at comparable points along the trajectory is used frequently to characterize differences in risk factors for developing an alcohol use disorder (AUD).

The two most widely supported subjective response models are the Low Level of Response Model and the Differentiator Model (Quinn and Fromme, 2011), using data derived at specific points along the breath alcohol concentration (BrAC) curve. The Low Level of Response Model, initially described by Schuckit, was based on the observation that males with a positive family history of alcoholism (FHP) reported lower subjective responses to an alcohol challenge than family history negative (FHN) males (Schuckit, 1980). Thus, it was hypothesized that low level responders consume more alcohol to achieve a particular effect, increasing their risk for the development of an AUD (Schuckit, 2009). Interestingly, the 30 and 60 minute post alcohol consumption time points, roughly corresponding to peak and descending limb alcohol concentrations, were most sensitive to familial differences in subjective response (Schuckit et al., 1996; Schuckit et al., 1997; Schuckit, 1980; Eng et al., 2005). Other investigators observed that the human response to alcohol has biphasic properties: more stimulating on the ascending limb and more sedating on the descending

limb of the blood alcohol curve after ingestion (Goldberg, 1943; Pohorecky, 1977; Newlin and Thomson, 1990; King et al., 2002; Newlin and Renton, 2010; King et al., 2011). The Differentiator Model, originally proposed by Newlin and Thomson, posits that FHP, compared to FHN subjects, are more sensitive to the subjective effects on the ascending limb which tend towards the “pleasurable, excitatory aspects of initial intoxication”, and more tolerant during the descending limb which may “attenuate the feelings of anxiety and depression that predominate as blood alcohol levels drop (Newlin and Thomson, 1990).” Consequently, the combination is thought to increase risk for the development of an AUD.

Recently, King and colleagues reported results of a prospective study that are consistent with a modified Differentiator Model. Future risk was associated with the relative STIMULATION and SEDATION response to alcohol on the ascending and descending BrAC limbs respectively (King et al., 2011; King et al., 2014; King et al., 2016), but did no family history effects were observed. They also presented evidence suggesting those responses, measured near peak BrAC concentrations, were sufficient to infer the degree of risk directly (King et al., 2011).

Others have compared subjective and other responses during the ascending and descending limb of the same alcohol response curve in order to assess acute adaptation to alcohol. Mellanby examined dependent measures of alcohol response on the ascending and then descending limbs of the same alcohol challenge (Mellanby and Committee, 1919). Acute tolerance to alcohol was defined as an improvement in performance on the descending limb; a decrement in performance as acute sensitization to alcohol. Using this approach, acute tolerance to alcohol has been identified to a variety of measures and associated with AUD and drinking related risk (see (Holland and Ferner, 2017) for a review). Recently and of note, McCarthy and colleagues found an association between the slope of the ascending limb and acute tolerance to subjectively assessed intoxication (Morris et al., 2017). Consequently, measurement or control of the breath (and therefore brain (Gomez et

al., 2012)) alcohol concentration trajectory is a key facet in the assessment of subjective (and other) responses to alcohol.

The foregoing research was based on ingestion of alcohol. Oral consumption is an ecologically valid approach, but its utility is challenged by an unavoidable 2-3-fold range of peak BrAC and latency to peak BrAC, encountered between participants (Figure 1 upper, (Ramchandani et al., 2009) among others). The range of variation in BrAC at any particular point in time is greatest on the ascending limb and at peak concentration, narrowing after absorption and distribution phases are completed as alcohol elimination dominates the pharmacokinetics. As a result, following ingestion, assessment of the brain's response to alcohol can be complicated by substantial variation in the independent experimental variable, BrAC trajectory (Schuckit, 1980; Schuckit et al., 1996).

Much of our own previous work has employed methods providing careful control of the BrAC trajectory; using intravenous (IV) alcohol administration to achieve nearly identical trajectories across subjects. Our laboratory's use of the IV route of administration began with the BrAC clamp (O'Connor et al., 1998; Ramchandani et al., 1999a; O'Connor et al., 2000), a paradigm in which each individual's BrAC is held constant at the same predetermined level for a prescribed interval, usually hours. Using such methodology, we have explored the relationship between biological family history (Ramchandani et al., 1999b; Morzorati et al., 2002; Ramchandani et al., 2002), genetic influence (Ramchandani et al., 2011; Kosobud et al., 2015), recent drinking history (Ramchandani et al., 2002; Gilman et al., 2012), sensitivity to the limb and rate of change of alcohol exposure (Wetherill et al., 2012), and other risk factors (Gowin et al., 2017), to subjective and physiological responses to alcohol.

Some of our findings regarding subjective perceptions from our BrAC clamping studies appeared to differ from studies by other investigators that employed an oral alcohol challenge. For example, in our largest clamping study, FHP individuals showed greater sensitivity to measures of SEDATION, INTOXICATION, and HIGH attributable to alcohol than FHN individuals and demonstrated the development of acute tolerance to alcohol in

subjective ratings of INTOXICATION and HIGH over the course of a 105 minute steady-state BrAC clamp. All subjects reported acute tolerance of perceived STIMULATION attributable to alcohol (Morzorati et al., 2002). One possible explanation for the discrepancy was that the route of alcohol administration influences the subjective response to alcohol, although another study using the IV alcohol clamp did not show FHP vs. FHN differences in alcohol response (Kerfoot et al., 2013).

We designed the current project to address the hypothesis that an individual's subjective responses attributable to alcohol do not differ by route of alcohol administration. One approach to test the hypothesis is to directly compare subjective responses following oral and IV alcohol administrations that produce similar BrAC trajectories within individuals (Figure 1 lower). Since it is impossible to adhere to a prescribed trajectory with oral alcohol dosing techniques, we chose to mimic each individual's oral BrAC trajectory with IV alcohol administration. We then collected subjective responses to alcohol, comprising SEDATION, STIMULATION, INTOXICATION, and HIGH measures, throughout the individually matched oral and IV BrAC trajectories.

## **Materials and Methods**

### *Study Design*

A total of 44 (22 male and 22 female), aged 21-30 years, healthy, non-alcohol dependent, non-treatment seeking, and alcohol-consuming subjects completed the study (Table 1) as described in (Ramchandani et al., 2009). This manuscript is based on data collected in the same study (2002 – 2003) as the Ramchandani, et al, 2009 paper which did not present any analysis of subjective perceptions and focused solely on the ability to mimic an individual's BrAC trajectory after ingestion by using infused alcohol. No other analyses have yet been performed on this dataset. As reported in that earlier paper, exclusion criteria were a clinically significant history of renal, hepatic, cardiovascular, pulmonary, or gastrointestinal disease, any DSM-III-R Axis I illness including substance dependence (1987),

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history of seizure or loss of consciousness, mental illness requiring hospitalization, or current use of psychoactive medication. Women were studied in the first 14 days following cessation of menses. Smoking was not an exclusion criterion, although subjects were not allowed to smoke once they arrived at the laboratory for the study session. Alcohol dependence was assessed with the Semi-Structured Assessment of the Genetics of Alcohol interview (Bucholz et al., 1994). Recent drinking history was determined with Timeline Follow Back (Sobell et al., 1988). Subjects were required to report a lifetime history of alcohol consumption, but no drinking constraints were placed upon their recent drinking history. All subjects provided informed consent for the protocol approved by the Institutional Review Board of the Indiana University School of Medicine. Each subject undertook 2 testing sessions in the same experimental setting on precisely the same time schedule, but on different days, separated by a minimum of 3 days as previously described in detail in (Ramchandani et al., 2009). All subjects had a zero BrAC measurement on arrival to the Clinical Research Center. Females provided a negative urine beta-hCG test for pregnancy prior to starting each session.

In both sessions, the subjects were aware they would receive alcohol, but, in an attempt to blind them to the route of administration, subjects both ingested a standard beverage and experienced an IV infusion. In the first session, the ingested beverage contained the dose alcohol that we had calculated to achieve a peak BrAC of 80 mg/dl, based on the individual's total body water and the nomogram published by Watson (Watson, 1989). The beverage, consisting of 95% alcohol diluted to a 20% by volume concentration with diet lemon-lime soda, was split into 4 aliquots with each consumed via a straw over 2 minutes. During that oral challenge session, we infused only Ringer's lactate at a constant rate of 30 ml/hr. In the second session, we infused 6.0% alcohol in Ringer's, using a pre-computed rate profile designed to replicate the BrAC trajectory recorded from that individual's the first session. The subject also ingested the same beverage volume, but with only 0.2 ml of 95% ethanol (0.8 grams of alcohol) on the top. As expected, BrAC trajectories

following ingestion of alcohol showed a high degree of between-subject variability (Figure 1 upper). However, our infusion methods, based on an individually-tuned, physiologically-based, pharmacokinetic model of alcohol distribution and elimination (Ramchandani et al., 1999a; O'Connor et al., 2000; Plawecki et al., 2008) demonstrated the ability to mimic each participant's BrAC exposure trajectory (Ramchandani et al., 2009) (Figure 1 lower).

During each session, subjects also undertook a battery of tests, including measures of subjective responses attributable to alcohol, saccadic eye movements, and resting electroencephalography. The full battery was repeated at baseline, during the ascending limb, and during the descending limb in both sessions, enabling comparison of the pharmacodynamics of similar exposures to alcohol. We assessed subjective response of the effects of alcohol at baseline and at 15 time-points after the start of alcohol administration: 12, 30, 45, 55, 75, 90, 105, 120, 125, 150, 165, 180, 195, 210 and 240 min. Here, we present the results comparing the subjective responses to orally and intravenously delivered alcohol producing equivalent BrAC trajectories within each subject.

#### *Assessment of Subjective Responses*

We used the Drug Effects Questionnaire (de Wit and McCracken, 1990; Gilman et al., 2008) modified to add the item INTOXICATION (Gilman et al., 2008), to assess HIGH and INTOXICATION via visual analogue scales consistent with our prior published work (Kosobud et al., 2015). We employed the Biphasic Alcohol Effects Scale (Martin et al., 1993) to assess SEDATION AND STIMULATION. These measures, like their underlying BrAC trajectories, demonstrated significant between-subject variability (Figure 2).

#### *Method for Calculating Latency and Magnitude of Dependent Measures*

Since BrAC trajectories varied significantly across subjects (Figure 1), the latency to peak BrAC for one subject could correspond to the ascending or even the descending limb in

another subject. Thus, if perception includes sensitivity to rising or falling BrAC, choosing the same elapsed time points for comparing responses across subjects would have contaminated all assessments. Consequently, as a first data processing step, we derived 3 specific assessment points from each session's BrAC trajectory. Spline-fitting Matlab® scripts determined the latencies corresponding to a session's peak BrAC and to the same, half-peak, BrAC on both ascending and descending limbs. We then computed corresponding subjective response magnitudes at those latencies, using linear interpolation between the nearest data-collection time points, and subtracted the corresponding baseline magnitude from each.

For each session and response, we also calculated the Mellanby effect; the descending limb response minus the ascending limb response derived at half-peak, within-session, BrACs (Holland and Ferner, 2017). We also employed the Matlab® function *integrate* to calculate the area under each session's entire subjective response curve (as collected, after baseline correction) for each response. The resulting subjective response dataset served all subsequent analyses.

### *Data Analysis*

To verify that both routes of alcohol administration produced their expected effects, mean response magnitudes at the peak BrAC for the 4 categories (SEDATION, STIMULATION, INTOXICATION, and HIGH) were compared to 0 using two-sided t-tests.

To address our hypothesis comparing subjective responses to alcohol by routes of administration, we employed two strategies: 1) to test for differences between Oral and IV responses and 2) to assess the similarity across the same measures. To test for differences, we used a repeated measures analysis of variance (ANOVA), with repeated factors including route (oral vs. IV) and BrAC trajectory location (the subject-dependent time points at which the relevant ascending limb, peak, descending limb BrAC exposures were obtained). We also used ANOVA for differences associated with the route of administration for the Mellanby

effect and area under the curve (AUC) measures, with route of administration serving as the sole repeated factor. An alpha of 0.0125 was used for each set of tests, correcting for 4 categories (SEDATION, STIMULATION, INTOXICATION, and HIGH), and sex was included as a covariate in all models.

To assess similarity, we computed Pearson correlation coefficients for the individuals' subjective responses at the 3 derived BrAC trajectory locations per session across routes of administration. There were 12 such computations per participant (3 measures from each of the 4 subjective responses) and we employed a corrected alpha level of 0.0042 to define significance. For both AUC and Mellanby effects, tests for significance of correlations were corrected for the 4 subjective responses examined; resulting in an alpha threshold of 0.0125.

## **Results**

### *Demographics and Subject Characteristics*

Table 1 presents the subject characteristics across the sample and divided by sex. All subjects tolerated study procedures well. There were neither significant adverse effects for oral nor IV alcohol administration.

All subjects tolerated all sessions well, without nausea or any other significant untoward effect. The most common reported side-effect was headache, which generally occurred at the end of the experimental session.

### *Verification of an Alcohol Effect*

Mean baseline corrected SEDATION, STIMULATION, INTOXICATION, and HIGH scores at peak BrAC were all significantly different from zero (all  $p < 0.0125$ ).

### *Differences in Subjective Responses by Route of Alcohol Administration*

Repeated measures ANOVA comparison at ascending limb, peak BrAC, and descending limb demonstrated no significant effect of route of administration for any subjective response (all  $p \geq 0.37$ , with one exception;  $p \geq 0.12$ , Figure 3 and Table 2). Repeated measures ANOVA comparison of the Mellanby effect and AUC demonstrated no significant effect of route of administration (all  $p \geq 0.23$ , with one exception;  $p \geq 0.08$ ; Table 3) for any subjective response. Further, there were no significant sex x route interaction effects (all  $p > 0.25$ ), indicating that males and females reported comparable subjective effects for both oral and IV alcohol administration.

### *Similarities in Subjective Responses by Route of Alcohol Administration*

Subjective effects for the measures of STIMULATION and HIGH were significantly correlated for all three comparison points (all  $p < 0.003$ ; Table 2, Figure 4). With the exception of SEDATION on the descending limb, the remaining SEDATION and INTOXICATION measures were well-correlated ( $p = 0.01$ ), but did not survive correction of significance threshold for multiple testing. The Mellanby effect and AUC correlations for each subjective response were all significantly correlated (all  $p < 0.005$ ; Table 3).

## **Discussion**

We have demonstrated that the route of alcohol administration does not yield appreciable differences in 4 subjective responses attributed to alcohol in a sample of young-adult drinkers. In other words, subjective pharmacodynamic effects of alcohol do not depend on the route of its administration following comparable trajectories of systemic alcohol exposure in that population.

We initiated this project in order to address a simple, but recurring question regarding our research – people drink alcohol, why administer it IV? A fundamental premise of our research has been that investigators should select the most appropriate methodology to answer the question at hand. For example, if one is studying the response to alcohol as a risk factor for subsequent escalation of drinking, BrAC exposure trajectory becomes an important variable of interest. An investigator must choose. One could choose to recruit a sample size sufficient to overcome the variability in alcohol exposure associated with oral consumption, and accommodate that variability in alcohol exposure in the interpretation of the resulting outcome. The other choice in human research is to minimize variability in brain exposure to alcohol with IV administration. Other factors apply to the investigator's choice, but having the option assumes the pharmacodynamics of alcohol do not vary by route of administration. The results of this experiment provide support for that argument.

This study compared subjective responses at the individual's peak BrACs as well as at equivalent BrACs on the ascending and descending limbs of the BrAC-time curve in a within-subject design. Our results suggest that, in this sample of young adult drinkers, subjects demonstrate substantial acute tolerance of STIMULATION to alcohol, moderate acute sensitization to SEDATION, and little acute adaptation to HIGH and INTOXICATION, when measured by the Mellanby method. However, without a placebo comparison, we cannot definitively state that these effects are not solely attributable to time and our experimental procedures. Importantly, there was no significant difference in these indices by route of alcohol administration. We note that the Mellanby method is subject to the debatable assumption that subjective sensitivity to the rate and direction of change (i.e. rising and falling) of BrAC plays no role in the phenomena assessed. Other methods for assessing adaptation are available; the BrAC clamp eliminates the rate of change (O'Connor et al., 1998, O'Connor et al., 2000, Ramchandani et al., 1999a) as a potential contributor, and other IV alcohol methods (Plawecki et al., 2012) allow for its control.

The within-subject nature of this study is an inherent strength. Even conservatively assuming a modest effect size of 0.3 (as measured by the Pearson correlation coefficient), this sample had 70% power to detect differences in the routes of administration. However, our results must be considered within the limitations of the study. First, this study necessarily includes the potential for an order effect. While we have demonstrated that it is possible to mimic an individual's BrAC trajectory following alcohol ingestion using IV infusion of alcohol (Ramchandani et al., 2009), it is impossible to achieve the opposite because of highly variable, uncontrollable alcohol absorption kinetics. Despite efforts to blind the subjects to the route of alcohol administration, it is possible that variable expectations associated with beverage characteristics impacted our data. However, even if they exist, such effects do not appear to be dramatic. If expectation was a major contributor, such effects would most likely be apparent on the ascending limb of the BrAC curve and substantial differences based on the route of alcohol administration were not observed. Within-individual responses were also quite similar at peak and descending BrAC despite the substantial variation across participants. Further, the means of the AUCs of subjective responses did not show a pattern indicative of session order.

Second, no placebo data were collected in this experiment. Thus, we cannot exclude any impact of our experimental setup and procedure upon subjective response. However, we believe that the within-subject analysis mitigates such concerns.

Third, our analysis is predicated on the assumption that an individual's pharmacodynamics of the subjective response to alcohol is stable, at least over the inter-session interval we used. The literature provides support that, at least for some individuals, the subjective response to alcohol is stable over a period of years and suggests that the overall structure of subjective response to alcohol is consistent across multiple testing sessions. King and colleagues have identified the subjective response to an oral alcohol challenge as a predictor of subsequent risk. They have reported consistency in the STIMULATION and SEDATION responses to alcohol at the estimated time of peak BrAC in

young-adult heavy drinkers tested twice over a 5 year follow-up interval (King et al., 2016).

While not examining individual subjective responses to alcohol, Lutz and Childs explored the latent structure of subjective responses in a cohort of moderate alcohol drinkers over six testing sessions (3 alcohol, 3 placebo) performed at 2-7 day intervals with timing described in (Childs and de Wit, 2016). They reported temporal stability of factors representing “Positive Mood,” “Sedation,” “Stimulation/Euphoria,” and “Drug effects and Urges” using an AUC based method (Lutz and Childs, 2017). Relatedly, Conrod et al. reported test-retest reliability in alcohol-induced heart rate variability, described as reflection of the stimulant properties of alcohol, in male subjects on the ascending limb of the blood alcohol concentration trajectory (Conrod et al., 2001).

Fourth, our protocol included 15 assessments of the subjective response to alcohol per route of administration. Given the significant variability in the BrAC trajectory attributable to oral alcohol administration, repeated subjective responses measurements were required to accurately capture the data. Thus, to minimize subject fatigue outside of the other dependent measure batteries, our subjective response assessment was limited to 4 items administered via computer. So, while each of these assessments can be completed in less than 10 seconds, it is possible that fatigue may have impacted the subjective response results. Further, dependent upon the time at which an individual subject reached their peak BrAC, a majority of the subjective response assessments may have been collected on the descending limb. However, our primary analysis of subjective responses at the ascending limb, peak, and descending limb assessment points used only one subjective response value each. This is also the case for the analysis of Mellanby acute adaptation. Thus, while the descending limb responses may have been over-weighted in the AUC analyses, we do not feel that, overall, our data collection strategy significantly prejudiced interpretation of our results.

Fifth, our subject sample comprised subjects who, on average, drank in moderation but reported a wide variation in their recent drinking history (see Table 1). We consider the wide range in alcohol consumption a strength of our study. We have no reason to suspect that drinking history would differentially impact the response to alcohol as a function of route of administration, but our study cannot exclude this possibility. Thus, extension of our within-subject results to other drinking populations is likely appropriate, but not assured.

Finally, extrapolation of this examination of subjective response to oral and IV alcohol to other dependent measures should be considered with caution. While we have no reason to hypothesize that other cognitive or behavioral measures would demonstrate a sensitivity to route of alcohol administration, we have not yet analyzed the other elements of our battery of dependent measures nor are aware of such analyses published by others.

We perceive that the results of this study should minimize any concern for individual differences in the pharmacodynamics of the subjective response to alcohol based on the route of alcohol administration.

*Author's contributions:* VAR and SOC were responsible for study concept, design, and execution. MP performed data fitting and calculation of dependent measures. MP, AD, JB and LW performed statistical analyses. MP, AD, VAR, and SOC drafted the manuscript. AK oversaw day-to-day lab operations and provided review of the manuscript for important intellectual content. All authors critically reviewed content and approved the final version for publication. None of the authors has any financial or intellectual conflict of interest in this research.

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*Invitation:* The infusion methodology used in this experiment has since been automated; investigators interested in adapting the capabilities of the Computer-assisted Alcohol Infusion System to their own research should send an email to oconnor1@iu.edu or mplaweck@iupui.edu.

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### Figure Legends

Figure 1. Breath Alcohol Concentration (BrAC) Trajectories after Oral (upper) and matched IV (lower) Administration of Alcohol. Substantial experimental variability in BrAC exposure trajectories, resulting from a carefully-controlled, individualized oral dose of alcohol intended to reach a peak BrAC of 80 mg/dl in 44 participants, is apparent (Ramchandani et al., 2009). Each oral dosage was determined for the individual based upon their total body water, and administered under identical experimental conditions. The oral alcohol challenge BrAC response variability was matched during the IV session (lower).

Figure 2. Subjective Response Trajectories after Oral and matched IV Administration of Alcohol. Substantial between-subject variability is apparent across the Sedation (row 1), Stimulation (row 2), Intoxication (row 3) and High (row 4) Subjective Response Measures in 44 participants to a carefully-controlled, individualized oral dose of alcohol intended to reach a peak BrAC of 80 mg/dl (left column) and subsequent IV session (right column) designed to match each individual's oral alcohol challenge breath alcohol concentration response curve.

Figure 3: Subjective Responses to Alcohol by Route of Administration. Responses (N=44 sample mean  $\pm$  sem) are displayed as baseline-corrected values at times corresponding to individual peak BrAC and half-peak points on the ascending and descending limbs. Sedation and Stimulation values were scaled by a factor of 10 for display purposes.

Figure 4: Subjective Response to Alcohol Correlations at Peak Breath Alcohol Concentration (BrAC) in Oral vs. IV administered alcohol sessions for 44 subjects. Sedation and Stimulation values were scaled by a factor of 5 for display purposes.

Table 1

	All Subjects (n = 44)	Females (n=22)	Males (n=22)
Age (years)	25.2 ± 0.4	25.6 ± 0.4	24.7 ± 0.6
Height (cm)	174.9 ± 1.7	166.9 ± 1.4	182.9 ± 1.9
Weight (kg)	78.9 ± 2.6	71.0 ± 2.4	86.7 ± 4.0
Total Body Water (L)	41.1 ± 1.4	33.3 ± 0.6	48.9 ± 1.5
Smokers (Number)	8	4	4
28 Day Recent Drinking History			
Drinks per Drinking Day (Standard Drinks/Day) [Range; Median]	2.9 ± 0.3 [0 - 8.7; 2.6]	2.4 ± 0.3 [0 - 7.7; 2.0]	3.5 ± 0.4 [1 - 8.7; 3.4]
Total Drinks (Number) [Range; Median]	22.2 ± 3.1 [0 - 90; 16]	18.6 ± 4.1 [0 - 75; 13]	25.5 ± 4.7 [1 - 90; 20]
Drinking Days (Number) [Range; Median]	7.5 ± 1.0 [0 - 28; 6]	7.3 ± 1.4 [0 - 28; 6]	7.8 ± 1.3 [1 - 25; 6]

Table 2

	Ascending Limb Correlation	Peak BrAC Correlation	Descending Limb Correlation	Trajectory Comparison p value
Sedation	0.41, <i>p</i> =0.01	<b>0.67,</b> <b><i>p</i>&lt;0.0001</b>	0.24, <i>p</i> =0.12	0.63
Stimulation	<b>0.69,</b> <b><i>p</i>&lt;0.0001</b>	<b>0.64,</b> <b><i>p</i>&lt;0.0001</b>	<b>0.44,</b> <b><i>p</i>=0.003</b>	0.73
Intoxication	0.38, <i>p</i> =0.01	<b>0.70,</b> <b><i>p</i>&lt;0.0001</b>	<b>0.61,</b> <b><i>p</i>&lt;0.0001</b>	0.37
High	<b>0.73,</b> <b><i>p</i>&lt;0.0001</b>	<b>0.78,</b> <b><i>p</i>&lt;0.0001</b>	<b>0.65,</b> <b><i>p</i>&lt;0.0001</b>	0.12

Table 3

	Subjective Response	Oral Alcohol Response	IV Alcohol Response	Pearson Correlation	p-value for Route of Administration
Mellanby Effect	Sedation	-1.53 (1.23)	-2.74 (1.02)	<b>0.42,</b> <b><i>p</i>=0.01</b>	0.34
	Stimulation	4.37 (1.52)	4.04 (1.68)	<b>0.82,</b> <b><i>p</i>&lt;0.0001</b>	0.74
	Intoxication	3.99 (2.55)	2.43 (2.87)	<b>0.57,</b> <b><i>p</i>&lt;0.0001</b>	0.54
	High	4.84 (2.6)	2.56 (4.49)	<b>0.73,</b> <b><i>p</i>&lt;0.0001</b>	0.23
AUC	Sedation	629 (213)	775 (288)	<b>0.57,</b> <b><i>p</i>&lt;0.0001</b>	0.55
	Stimulation	221 (225)	504 (261)	<b>0.56,</b> <b><i>p</i>&lt;0.0001</b>	0.23
	Intoxication	4790 (477)	4340 (550)	<b>0.69,</b> <b><i>p</i>&lt;0.0001</b>	0.29
	High	4403 (498)	4403 (498)	<b>0.75,</b> <b><i>p</i>&lt;0.0001</b>	0.08

Table Legends:

Table 1: Demographics and Subject Characteristics. All values are Mean +/- Standard Error of the Mean (SEM). Italicized font indicates significant difference from men at  $p = 0.05$ .

Table 2: Correlations of within-subject Subjective Responses to Alcohol at individual Peak (column 2) and half-Peak BrAC time points on the ascending and descending limbs (Columns 1 and 3, respectively), for Oral vs. IV routes of alcohol administration. BrAC point and Trajectory Comparisons. Column 4 displays the p-values for Repeated Measures ANOVA p-values for the trajectory consisting of those three points. Italics indicate significance at  $p = 0.05$  level; Bold indicates significance at  $p = 0.0042$ .

Table 3. Comparisons across ORAL vs IV route of alcohol administration of the Mellanby Effect and Area Under the Curve for Stimulation, Sedation, Intoxication, and High Subjective Response to Alcohol. Mellanby and AUC values are presented as mean (SEM). Pearson correlation coefficients and the Repeated Measures ANOVA p-values for the route of administration are displayed. Bold font indicates significance at  $p = 0.0125$ .

Figure 1

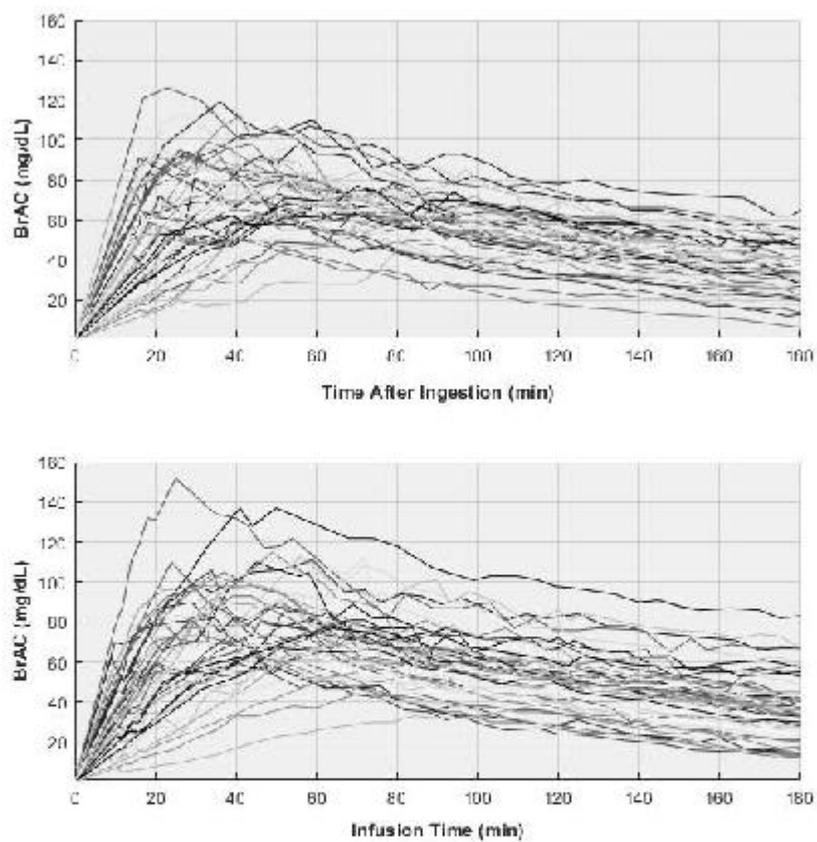


Figure 2

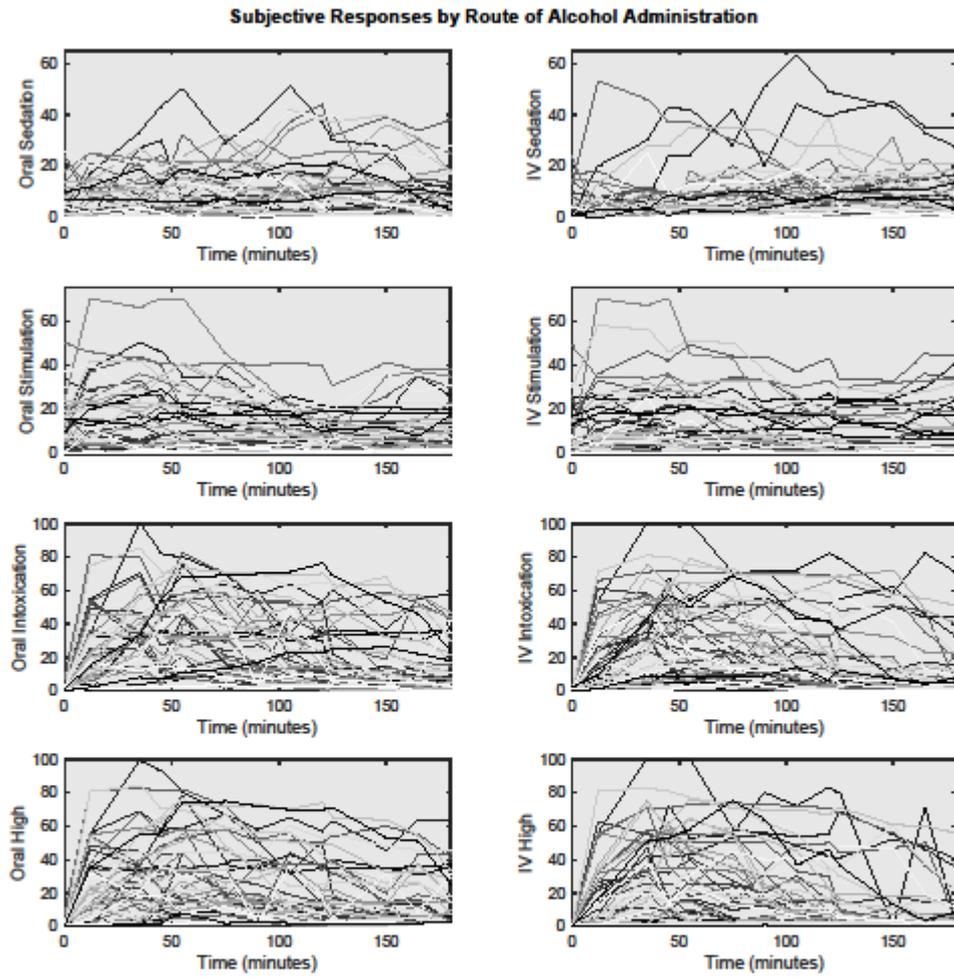


Figure 3

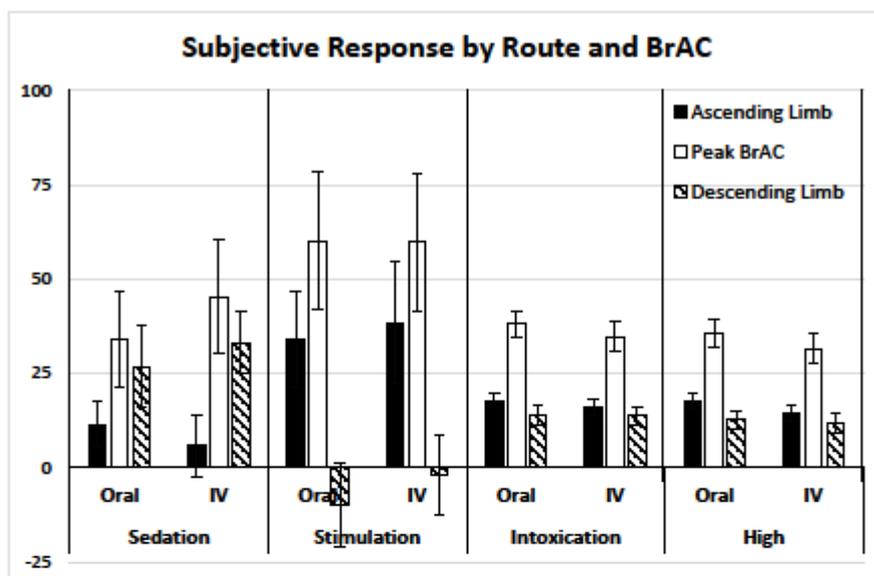


Figure 4

